Fetal Thyroid Volume in the Normal and Thyrotoxic Pregnancies

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Abstract

A prospective study of the thyroids of 289 normal fetuses was performed sonographically to establish normal values of fetal thyroid volume for the gestational period between 20 and 36 weeks. The lengths of the three longest axes of each thyroid lobe were measured for the calculation of the volume of separate lobe by the Ellipsoid equation (V = Thickness x Width x Length x π/6). The volume of the isthmus was estimated as being 5% of the volume of both lobes. The FTV was the sum of the volume of both lobes and the isthmus. Another 72 fetal thyroids from those mothers with past or active Graves' disease were evaluated and compared to the normal values.

The normal fetal thyroids were found to increase with gestational age in an exponential manner. This agreed with the maturation process of the fetal thyroid reflected by the fetal total T_4 concentrations shown in published studies. The mean ($\pm$SD) FTV was 0.23 $\pm$ 0.18 cm^3 (range: 0.022cm^3 - 0.85cm^3; median 0.17cm^3). The rate of growth was fastest during late gestation being 0.054cm^3/week after 32 weeks as compared to 0.051cm^3/week and 0.055cm^3/week in the treated and untreated groups of the thyrotoxic population at the corresponding period of gestation.

All 72 FTVs in this thyrotoxic population were all within the normal range. The trend of FTVs in the treated group was relatively constant around the mean independent of the maternal thyroid status while the FTVs

in the untreated group varied over a wider range within the normal limits. It seems that antithyroid treatment regularizes the fetal thyroid growth in thyrotoxic mothers, but that immunoglobulins may still affect the fetus and neonate in mothers with a past history of thyrotoxicosis.

The mean fetal thyroid volume to estimated fetal weight (V/W) ratio (± SD) in the normal fetuses was relatively constant throughout the gestation equal to 0.163 ± 0.079 cm^3/kg which was smaller than those for the child and the adult reported in the literature. The difference suggested that fetal thyroid enlargement underestimation may occur if postnatal criteria were used. The mean value under 36 weeks (0.161 ± 0.080 cm^3/kg) was significantly smaller than that over 36 weeks (0.200 ± 0.061 cm^3/kg). This finding may indicate that the fetal thyroid gland grows more near term in preparation for the role of thermogenesis in the postnatal life, in addition to stimulating growth and development of the central nervous system antenatally. The range of z scores of the V/W ratios was significantly narrower and the values smaller in the treated than in the untreated group implying that this group of fetuses was less prone to have fetal goiter.

Low birth weight infants were more frequent in the thyrotoxic population than in the normal population with a percentage of 11.5 in which LBW infants were predominantly in the treated group. Although treatment may regularize fetal thyroid growth, it does not seem to ensure normal fetal growth. Therefore, careful monitoring of fetal thyroid and somatic growth

throughout the pregnancy by serial fetal ultrasound is crucial. The nomogram and normal reference for fetal thyroids in this study should be useful to help achieve the best possible outcome.

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Abbreviations

AC	Abdominal Circumference
AMC	Antimicrosomal Autoantibodies
ATG	Antithyroglobulin Autoantibodies
BPD	Biparietal Diameter
CMZ	Carbimazole
EFW	Estimated Fetal Weight
fT_4	Free Thyroxine
FL	Femur Length
FTV	Fetal Thyroid Volume
GA	Gestational Age
IUGR	Intrauterine Growth Retardation
LBW	Low Birth Weight
$L\text{-}T_4$	Levothyroxine
MMI	Methimazole
PTU	Propylthiouracil
T_3	Triiodothyronine
T_4	Thyroxine
TIIg	Thyroid-inhibitory Immunoglobuin
TRH	Thyrotropin-releasing Hormone
TSAb	Thyroid-stimulating Hormone- receptor Antibodies
TSH	Thyroid-stimulating Hormone
TSIg	Thyroid-stimulating Immunoglobulin
sTSH	Sensitive Thyroid-stimulating Hormone
V/W	Fetal Thyroid Volume to Estimated Fetal Weight Ratio

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Background

Graves' disease is the commonest cause of hyperthyroidism in pregnancy (Becks & Burrow 1991), particularly so in the East including Hong Kong. It is well recognized that adverse effects of the disease itself and its medical treatment by antithyroid drugs may lead to either fetal hyperthyroidism or hypothyroidism. The affected fetus may present with a spectrum of abnormalities in which fetal goiter and/or intrauterine growth retardation (IUGR) are common. If fetal thyroid dysfunction is undiagnosed in utero, it may significantly increase fetal and neonatal morbidity and mortality (Becks & Burrow 1991, Sipe & Malee 1992, Polk1994, Seely & Burrow 1994).

As the infants of thyrotoxic mothers have a higher risk for thyroid dysfunction in association with a variety of abnormalities, early in-utero diagnosis is mandatory so that maternal therapy could be adjusted. If necessary, even fetal therapy could be instituted.

Unfortunately, there is no satisfactory indicator for fetal thyroid function. Abnormal fetal heart rate and IUGR are too poorly correlated with fetal thyroid status to be used as indicators for abnormal thyroid function (Wallace et al 1995).

Fetal goiter is specific for fetal thyroid disease, fetal thyroid volume may give an indication of possible fetal thyroid disorder. However, the data

available in the literature for fetal thyroid dimension are limited to those established by Bromley et al of fetal thyroid width and fetal thyroid circumference (Bromley et al 1992). However, this study included the trachea in the measurements. Furthermore, these data could not be compared with postnatal thyroid volumes which have been recorded in all other age groups.

The objectives of this study therefore were to establish a nomogram for fetal thyroid volume (FTV) related to gestational age, to evaluate the relationships of FTV to other growth parameters, to calculate the growth rate of normal fetal thyroid glands, to obtain the value of Fetal Thyroid Volume to Estimated Fetal Weight (V/W) ratio which is a parameter commonly used in the paediatric and adult population, and to compare the FTVs in the normal population against those in the thyrotoxic population, with an aim of providing a normal reference of FTV for the evaulation of possible fetal thyroid disorder.

Chapter 1 Introduction

1.1 Thyrotoxicosis

Thyrotoxicosis is a syndrome produced by excessive quantities of either endogenous or exogenous thyroid hormone, while the term `hyperthyroidism' is used to denote only those conditions in which sustained hyperfunction of the thyroid leads to thyrotoxicosis (Braunwald et al 1987). Thyrotoxicosis is common in pregnancy with reported incidences ranging from 0.04% to 1.4% (average 0.2%) (McDougall 1989). The aetiology of thyrotoxicosis in pregnancy includes Graves' disease, toxic multinodular goiter, toxic adenoma, trophoblastic neoplasia, pituitary hypersecretion of TSH, metastatic follicular cell carcinoma, De Quervain's thyroiditis, silent lymphocytic thyroiditis and struma ovarii (Table 1).

Asian women more frequently develop biochemical evidence of thyrotoxicosis at the beginning of the second trimester than the Caucasians and are at greater risk of clinically apparent gestational thyrotoxicosis (Price et al 1996). It is estimated that about 90 to 95 per cent of thyrotoxicosis in pregnancy is due to Graves' disease (Braunwald et al 1987; Seely & Burrow 1994). However, with our local experience, Graves' disease appears to be even more frequent than the reported figure as the cause of gestational thyrotoxicosis in this population.

Subclinical hyperthyroidism is defined as serum thyroid hormone levels in the reference range with low serum TSH concentrations. The causes include subacute thyroiditis, iodine-induced hyperthyroidism, toxic thyroid nodule and Graves' disease with Graves' disease being the commonest (Charkes 1996). It has been reported that the frequency of subclinical hyperthyroidism is higher in Southeast Asians (Weigle et al 1996)

Table 1. Aetiology of Thyrotoxicosis in Pregnancy

Common	Uncommon	Rare
Graves' disease	Toxic multinodular goiter	Hypersecretion of TSH
	Thyroiditis	
	Toxic adenoma	
	Functioning follicular carcinoma	
	Struma ovarii	
	Trophoblastic neoplasia	

1.2 Graves' Disease

Graves' disease is a syndrome which usually includes hyperthyroidism, a diffusely enlarged thyroid and in some patients ophthalmopathy, dermopathy, finger clubbing and acropachy. The eponym derives from Robert Graves' description in 1835 of three women with goiter, palpitations, forceful heart beat, and tachycardia. Complications of Graves' disease include atrial fibrillation, tachyarrhythmias, periodic paralysis which is common in Oriental men, protracted vomiting and, if severe, can progress to thyroid storm (McDougall 1991). Thrombocytopenia and hepatitis have also been reported in a Chinese man with relapse Graves' disease (Szeto et al 1997).

The aetiology of Graves' disease is incompletely understood but it is associated with different HLA genes in Caucasians and the Chinese, in whom the HLA associations may be stronger in males than females. It has been shown that the positive HLA associations in the Hong Kong Chinese are different from those in Caucasians whereas the protective haplotype is similar to that described in Caucasians (Cavan et al 1994).

Graves' disease is more frequent in women of reproductive age (Braunwald et al 1987). It is an organ-specific autoimmune disorder mediated by a group of antibodies that bind to the TSH receptor on thyroid follicular cells. This binding effectively stimulates increased thyroid hormone biosysthesis and secretion. The action of the circulating immunoglobulins

on the TSH receptor are mostly stimulatory but can also be inhibitory (Smith et al 1988, Sipe & Malee 1992). It is possible that patients with Graves' disease may develop hypothyroidism due to Hashimoto's disease or vice versa (Tamai et al 1990, Takasu et al 1990). However, there is no single immunological abnormality which can explain all of the clinical features (McDougall 1991).

Ideally, hyperthyroid women should be rendered euthyroid before considering conception. The incidence of maternal, fetal and neonatal morbidity is significantly higher in those patients whose hyperthyroidism is not medically controlled. Maternal morbidity includes a higher incidence of toxemia, premature delivery, congestive heart failure and thyroid storm. Neonatal morbidity includes small-for-date neonates, prematurity, neonatal hypothyroidism or hyperthyroidism. Fetal goitre is occasionally reported in infants of thyrotoxic mothers (Mestman 1997).

Pregnancy may have a favourable effect on the course of Graves' disease particularly in the second and third trimesters, but there is a tendency for relapse postpartum, usually two to three months postpartum (Amino et al 1982). The immune tolerance that develops during pregnancy is primarily maternal-placental tolerance rather than maternal-fetal tolerance. (Colbern & Main 1991).

1.3 Laboratory Assessment of the Mothers

Ever since the introduction of immunometric assays (IMAs) for serum thyrotropin in 1980s and subsequent sensitive sTSH assays, they have been advocated as an initial test for thyroid dysfunction. The enhanced sensitivity of these tests permits earlier detection of minor thyroid dysfunction. The sensitive sTSH assays allow discrimination of the very low TSH levels encountered in hyperthyroidism from those found in healthy euthyroid individuals. It can also facilitate fine tuning of LT_4 replacement therapy and monitoring of T_4 suppression therapy. With the highly sensitive chemiluminescent assay which demonstrates an eight- to ten-fold increase in sensitivity over a sensitive IMA, not only can hyperthyroidism be distinguished from euthyroidism, but also degrees of TSH suppression in subclinical hyperthyroidism can be detected (Ross et al 1989). The TRH stimulation test in favour previously is now effectively redundant as hyperthyroidism can be excluded by a sTSH test (Klee & Hay 1987; Bayer 1991). Therefore, sTSH was preferred to fT_4 in the determination of maternal thyroid status in the mothers who are not on antithyroid treatment .

An elevated serum free T_4 and a suppressed TSH are diagnostic of hyperthyroidism. It has been suggested that TSH values <0.05μU/ml are indicative of hyperthyroidism in the absence of pituitary disease (Seely & Burrow 1994, Burrow 1995). It is important to differentiate Graves' hyperthyroidism from other causes of hyperthyroidism because the

management of Graves' disease and its potential effects in pregnancy on the infants are different from other hyperthyroid states.

The most useful laboratory test to confirm or exclude autoimmune disease in terms of speed and cost is measurement of thyroglobulin (ATG) and microsomal (thyroid peroxidase)(AMC) autoantibodies. These antibodies are positive in about 80% of patients with Graves' disease or Hashimoto disease which may exist without circulating antibodies (Kaplan 1985, Bayer 1991, Weetman 1994).

By haemagglutination of red cells coated with the antigen of interest, between five to ten per cent of normal individuals, especially older women, have a weakly positive titer in each test. In patients with thyroid disease, many have only elevated AMC antibody titers, some have elevated titers of both and a few have only elevated ATG titers (Kaplan 1985).

Elevated titers in an euthyroid or hypothyroid patient suggest Hashimoto's thyroiditis whereas in a hyperthyroid patient Graves' disease is the most likely diagnosis.

Routine antibody testing will be more effective when sensitive immunoassays are used instead of haemagglutination procedures, although the findings of thyroid antibodies may still not be in concordance with the clinical findings in either method. The clinical utility of immunological

investigations may include prediction of the risk of congenital hyperthyroidism in infants of a pregnant mother with Graves' disease; confirmation of a transient neonatal hypothyroidism; prediction of relapse of hyperthyroidism after medical therapy, and differential diagnosis of euthyroid Graves' disease versus orbital tumour (Bayer 1991). Only the first two uses are relevant in this study.

1.4 Placental Transfer

If a woman who had been or is suffering from Graves' disease becomes pregnant, her fetus will be at risk of thyroid dysfunction because there are a number of maternal thyroid and anti-thyroid agents which can pass through the placenta and affect fetal thyroid function.

In a normal pregnancy, the fetus is essentially protected from the effect of maternal thyroid physiology because the placenta is impermeable to TSH throughout the pregnancy. The effectiveness of placental transfer of T_4 and T_3 is controversial. Earlier studies showed that the placenta was only minimally permeable to T_4 and T_3 at the early stages of gestation (Roti et al 1983, Fung et al 1986, Polk 1994). However, Vulsma et al have shown that placental transfer of T_4 and T_3 does occur at term in a significant amount that may be essential to achieve normal cerebral development. They measured the serum levels of T_4 of 40 infants with congenital hypothyroidism (25 with a total organification defect and 15 with thyroid agenesis) at birth and showed that a developmentally significant but subnormal level of T_4 was present in those infants. The subnormal T_4 level was between 35 to 70 nmol/litre as compared to the normal range 80 nmol/litre to 170 nmol/litre (Vulsma et al 1989).

A recent study has reported that although placental transport of iodothyronines is limited, significant maternal-fetal transfer of T_4 occurs, accounting for approximately 30% of the average 10μg/dL serum-T_4

concentration in fetal-cord blood at term. This maternal contribution to the fetal-T_4 is important for normal fetal maturation, particularly of the central nervous system, both at early gestation before the fetal thyroid gland is capable of thyroid hormone systhesis and at late gestation when thyroid hormones act on multiple organs (Fisher DA 1997).

In thyrotoxic pregnancies, there are both endogenous and exogenous influences. The endogenous effect comes from maternally produced immunologlobulins and the exogenous influences are related to the therapies that may be applied.

The placental permeability to various agents is listed in Table 2. Iodides, thyrotropin-releasing hormone (TRH), TSH-receptor antibodies (TSAb): thyroid-stimulating immunoglobulins (TSIg) and thyroid-inhibitory immunoglobulins (TIIg), and thionamide drugs eg. propylthiouracil (PTU) and carbimazole (CMZ) can cross the placenta. In contrast, the placental permeability to TSH and thyroid hormones is relatively low (Burrow 1995) .

Table 2. Placental Transfer of Maternal Thyroid and Antithyroid Agents

	Placental Transfer		
	High	***Low***	***No***
Normal (Endogenous)	TRH	T_3 & T_4	TSH
Abnormal (Endogenous)	TSAb (TSIg &TIIg)	T_3 & T_4	TSH
Exogenous	Iodides Thionamides TRH	T_3 & T_4	-

1.5 Effects of Maternal Thyroid and Antithyroid Agents on the Fetus

Under the effects of maternal thyroid agents and antithyroid treatment, it is estimated that 2 to 12 % of fetuses or neonates born to mothers with Graves' disease will develop either hyperthyroidism or hypothyroidism (Wenstrom et al 1990). In Asia, the incidence seems to be much lower. No fetal goitre was detected in a six-year review on 28 cases of hyperthyroidism complicating pregnancy in Malaysia (Lim et al 1989) and in a 12-year review on 114 cases with same clinical history in Thailand (Phuapradit et al 1993).

1.5.1 Thyroid-stimulating Immunoglobulins (TSIg)

Graves' disease (autoimmune thyrotoxicosis), the commonest cause of hyperthyroidism in pregnancy, is a result of TSIg binding to and stimulating the TSH receptor (McDougall 1989). Thyroid-stimulating Immunoglobulins cross the placenta easily and may cause fetal and/or neonatal thyrotoxicosis which occurs in about 1% of babies born to women with a history of Graves' disease or Hashimoto's thyroiditis (Becks & Burrow 1991, Shulman & Root 1991, Seely & Burrow 1994). Congenital hyperthyroidism is usually transient, lasting only three to 12 weeks after birth and is independent of the mother's current thyroid status. The risk is probably greatest in fetuses of mothers who have had previous ablative thyroid treatment as the fetus may be exposed to TSIg throughout the

gestation and may remain unrecognized (Sipe & Malee 1992). Delayed onset is not uncommon and may become chronic as congenital Graves' disease (Becks & Burrow 1991).

Fetal thyrotoxicosis is suggested by a heart rate greater than 160 beats/min, growth retardation, advanced bone age, premature craniosynostosis, fetal goiter and frontal bossing (Becks & Burrow 1991, Belfar et al 1991). In severe cases, fetal thyrotoxicosis may lead to with intrauterine death with pathologic findings including pulmonary hypertension, visceromegaly, generalized adenopathy, decreased subcutaneous fat and thyromegaly (Page et al 1988). Fetal loss in untreated cases approaches 50% (Bruinse et al 1988).

1.5.2 Thyroid-inhibitory Immunoglobulins (TIIg)

Patients with Graves' disease can occasionally develop hypothyroidism from switching TSH-receptor stimulating antibodies to TSH-receptor inhibitory antibodies. Graves' disease and Hashimoto's thyroiditis can present together in a condition referred to as "hashitoxicosis". Transient hypothyroidism after spontaneous resolving Graves' disease may present despite increasing TSAb activity (Shigemasa et al 1990). Although TSH-blocking antibodies cross the placenta readily, they play little role in affecting the development of congenital hypothyroidism. This has been shown by a study of the immunoglobulins from 15 mothers of infants with congenital hypothyroidism. Only one out of 15 of these immunoglobulins exhibited TSH-inhibitory activity and was able to block TSH-stimulated iodine organification in vitro. This immunoglobulin could inhibit TSH action by 30-50% in utero, but could not block radiolabelled TSH from binding to its receptor. The inhibitory action was only on dibutyryl cyclic AMP stimulation of iodine organification implying a unique effect on post-receptor processes (Ginsbery et al 1986).

1.5.3 Thionamides (antithyroid drugs)

The thionamide drugs are used most commonly for treatment of thyrotoxicosis during pregnancy. PTU and CMZ are the two prinicipal thionamides that have been used interchangeably (Thorpe-Beeston & Nicolaides 1996). Both PTU and CMZ will inhibit thyroid hormone biosynthesis by preventing organification of iodide and coupling of iodotyrosines to form T_4 and T_3 but PTU can inhibit extrathyroidal conversion of T_4 to T_3 and lower T_4 levels faster than CMZ (Sipe & Malee 1992). PTU has no known side effect of aplasia cutis in the offspring as has occurred with MMI, an active metabolite from CMZ (Van Herle et al 1975; Stephan et al 1982; Kalb & Grossman 1986; Burrow 1995). All thionamides cross the placenta easily and are excreted into the breast milk. But the placental transfer of PTU is four times less and the excretion of PTU into breast milk is ten times less than that of CMZ (Cooper 1984; Cooper 1987).

In spite of all these advantages, PTU tends to accumulate in the fetus because of low fetal clearance and this may lead to fetal hypothyroidism (Polk 1994). It had been reported that fetal T_4 levels were lower in mothers under thionamides treatment when compared to those in remission who were off treatment (Momotani et al 1986). Cheron et al discovered a lower T_4 level in 11 babies who were born to mothers on combined antithyroid-drug treatment in which a higher doses of PTU were used (Cheron et al 1981).

Methimazole has been associated with a reversible scalp defect, aplasia cutis, in the fetus (Stephan et al 1982). Placental transfer of thionamides during maternal drug therapy may also induce in-utero hypothyroidism or exhibit transient neonatal hypothyroidism. The incidence of transient hypothyroidism in exposed infants varies from 1% (Blackburn & Loper 1992, Burrow 1995) and to about 10% in iodine-deficient endemic areas (Becks & Burrow 1991). Infants exposed to antithyroid drugs in utero may develop a small goiter (Becks & Burrows 1991). A hypothyroid fetus may also present with bradycardia, intrauterine growth retardation (Seely & Burrow 1994) and is at risk of neurologic deficits (Rovet et al 1987, Heyerdahl et al 1991).

1.5.4 Iodides

Iodides can readily cross the human placenta. Although iodine is essential for fetal thyroid hormone synthesis, excessive iodine levels may cause iodide-induced fetal hypothyroidism and goiter. Such levels may result from maternal ingestion of iodine-containing proprietary medications for treatment of respiratory symptoms or administration of iodides for treatment of maternal thyrotoxicosis. In contrast to thionamides, iodides may produce a relatively greater fetal goiter which is likely to become obstructive (Galina et al 1962) because the mechanisms that protect against iodine excess (the Wolff-Chaikoff effect) do not develop in the fetus until near term (Shulman & Root 1991, Polk DH 1994).

1.5.5 Thyrotropin Releasing Hormone (TRH)

Despite the high permeability of TRH to the placenta, the levels of endogenous TRH in maternal blood are too low to affect fetal thyroid function. However, maternally administered exogenous TRH is effective in increasing fetal levels of TSH and thyroid hormones. As the term fetal human pituitary is extremely sensitive to the TSH stimulatory effect of exogenous TRH, fetal serum TSH concentration will rise and stimulate fetal thyroid to release both T_3 and T_4 (Roti et al 1981). These findings led to the later wide investigation of the therapeutic role of exogenous TRH to promote lung maturity in preterm fetuses (Morales et al 1989).

1.6 Diagnostic and Screening Tests for Fetal Thyroid Dysfunction

Fetuses at risk of thyroid dysfunction are those of mothers who have either a current or a previous history of Graves' disease. Correct diagnosis of fetal thyroid dysfunction must be made before fetal treatment can be instituted. Invasive tests allow confirmation of fetal thyroid abnormalities as well as direct treatment and are preferred to the less exact clinical parameters such as fetal heart rate and weight loss for establishing the right diagnosis.

The invasive diagnostic tests suggested in the literature involve indirect determination of fetal thyroid status via amniotic fluid sampling or direct quantification via cordocentesis. An elevated reverse T_3 (rT_3) or TSH level in the amniotic fluid may indicate fetal hyperthyroidism or hypothyroidism respectively (Kourides et al 1984, Yoshida et al 1986). Unfortunately, this method has considerable overlap between the euthyroid and hyperthyroid or hypothyroid ranges (Klein et al 1980). A study of measurements of amniotic fluid concentrations of iodothyronines and TSH reported that these parameters in amnotic fluid did not reliably predict fetal thyroid status in pregnancies complicated by maternal thyroid disorders or anencephaly. The former included two mothers with untreated hyperthyroidism, one untreated hypothyroidism, five hyperthyroid mothers on PTU and three hypothyroid mothers on LT_4 replacement (Hollingsworth &

Alexander 1983). Cordocentesis is more accurate compared to the relatively insensitive amniotic fluid sampling in predicting fetal thyroid status (Porreco & Bloch 1990, Davidson et al 1991; Polk 1994; Van Loon et al 1995).

Measurement of maternal serum TSIg may give a clue to fetal hyperthyroidism. Ultrasound evaluation of fetal heart rate, growth rate, bone age and the presence of goiter can be an adjunct to the definitive diagnosis of fetal dysfunction (Polk 1994) (Table 3).

Cord blood assay at delivery is widely employed as a neonatal screening method for congenital hypothyroidism (Daussault et al 1975, Lo & Lam 1996), but the assessment and treatment of neonates based on cord blood at delivery may already be too late to prevent intellectual impairment (Thorpe-Beeston & Nicolaides 1996).

Table 3 Ultrasonic Signs of Possible Fetal Thyroid Dysfunction

Fetal Hyperthyroidism	Fetal Hypothyroidism
1. Goiter	1. Goiter
2. Fetal heart rate > 160 beats/min	2. Bradycardia
3. IUGR	3. IUGR
4. Advanced bone age	
5. Premature craniosynostosis	
6. Frontal bossing	

1.7 Fetal Treatment

1.7.1 Fetal Hyperthyroidism

Due to the high placental permeability of thionamide drugs, fetal hyperthyroidism resulting from maternal immunoglobulins can be treated by maternal oral administration of antithyroid drugs (Polk 1994). It is believed that most cases of fetal hyperthyroidism will be treated if the mother is also receiving antithyroid drugs for Graves' disease. The dose that maintains the mother's thyroxine level in the high normal or slightly elevated range for pregnancy appears optimal for fetal thyroid function (Momotani et al 1986). In euthyroid mothers, thionamide drugs can still be prescribed to treat the fetus if fetal thyrotoxicosis has been diagnosed (Bruinse et al 1988).

Monitoring of the fetal response to therapy by ultrasonic signs such as fetal heart rate > 160 beats/min and IUGR is sensitive. Cordocentesis has been suggested to be the definitive method for diagnosis and assessment of response to treatment in fetal hyperthyroidism (Wallace et al 1995), however the need for definitive biochemistry must be balanced against the risk of the procedure which is less than 1% of perinatal loss in experienced hands (Weiner 1988) but could be higher in those with less experience.

1.7.2 Fetal Hypothyroidism

In utero therapy for suspected fetal hypothyroidism is difficult. Oral treatment of the mother with T_4 is ineffective because placental transfer of the hormone is inadequate for successful treatment of the fetus (Perelman & Clemons 1992; Seely & Burrow 1994). Other possible fetal therapies for fetal hypothyroidism include intra-amniotic (Lightner et al 1977), fetal intravascular and intramuscular injections (Van Herle et al 1975) of T_4 . The dose of L-T_4 required for adequate replacement is higher for intramuscular injection. The intraamniotic approach is generally preferred because of the simplicity of the procedure and the longer intervals between administration (Thorpe-Beeston & Nicolaides 1996).

The appropriate time for initiation of treatment as well as the appropriate dose of T_4 for treatment of fetal hypothyroidism remain speculative. No information is available regarding the pharmacokinetics of human fetal absorption of T_4 from amniotic fluid. Treatment regimens used are thus arbitrary (Perelman & Clemons 1992). Lightner et al successfully treated a hypothyroid fetus with weekly intraamniotic injections of 500μg of T_4 (Lightner et al 1977). Weiner et al treated a similar fetus with a single dose of 200μg of T_4 with reduction of fetal thyroid size (Weiner et al 1980). Perelman et al ultilized the dose of 500μg of T_4 every ten days to successfully ameliorate the fetal thyroid status (Perelman et al 1990). The optimal frequency and dosage of T_4 administration are still not established.

Indirect prenatal therapy can also be adopted successfully and safely by continuous maternal administration of the thyroid analogue 3,5,3'-triiodothyroacetic acid (Triac) (Nicolini et al 1996). Normalization of fetal thyroid function and reduction of fetal goiter may be achieved.

In fetal therapy, reduction of fetal goiter is a useful sign to suggest the effectiveness of the treatment applied. However, the method of fetal thyroid measurement is not consistent in the literature. Some measured the thyroid gland as if the goiter is a neck mass, others measured diameters or may follow Bromley et al (Avni et al 1992; Hatjis 1993; Hadi et al 1995).

1.8 Aims and Objectives of the Research

1.8.1 Aims

- To evaluate the feasibility of fetal thyroid volume estimations in pregnancy at all gestational ages.

- To provide a normal reference of the fetal thyroid volume (FTV) for the evaluation of possible fetal thyroid disorders secondary to maternal hyperthyroidism.

- To demonstrate the effects of maternal Graves' disease on the fetal thyroid gland.

1.8.2 Objectives

- To establish nomograms for the FTVs

- To determine the growth rate of normal fetal thyroids at different gestational age intervals

- To calculate the value of normal FTV to estimated fetal weight ratio (V/W) and compare with published data of the paediatric and adult population

- To compare the FTVs, its growth rate and V/W ratio in the normal population with those in a thyrotoxic population[1] grouped into
  - i. treated/ normal maternal thyroid function
  - ii. treated/ abnormal maternal thyroid function
  - iii. untreated/ normal maternal thyroid function
  - iv. untreated/ abnormal maternal thyroid function

[1] In this study, thyrotoxic population refers to all pregnant women with current or past history of Graves' disease with or without antithyroid drug treatment.

Chapter 2 Subjects and Methods

2.1 Patients' Profile

2.1.1 Normal Population

From December 1994 to May 1996, a total of 289 fetal thyroid glands were measured between 20 and 36 weeks of gestation in 289 mothers who had no known history of previous or current Graves' disease. All of them were referred from either the Obstetrics and Gynaecology department at the Prince of Wales Hospital or the Maternity and Care Health centres for ultrasound dating of gestation. Multiple gestations and any pregnancies complicated by maternal diabetes, hypertension, SLE and smoking were excluded from the study. Only one measurement from each pregnancy was used to establish the nomogram.

2.1.2 Thyrotoxic Population

From September 1995 to March 1997, a total of 184 fetal thyroid measurements were made between 20 and 36 weeks of gestation in 72 mothers who had either a current or a past history of Graves' disease. The patients were referred mainly from the Thyroid Clinic of the Medical Unit and a few from the Obstetrics and Gynaecology department. Fifty-one mothers (70.8%), in addition to the thyrotoxic symptoms, had laboratory proven autoimmune thyroid disease with TSAb present in their serum prior to or during pregnancy and the rest presented clinically without serum TSAb.

The thyroid status of the mothers varied. It could be euthyroid, hyperthyroid or hypothyroid. They had either received antithyroid drug treatment (eg. PTU or CMZ) due to their current thyrotoxic symptoms before the ultrasound scan or remained untreated as remission of the disease had occurred. In the latter, some were on L-T_4 replacement post thyroidectomy or post radioactive-I_{131} thyroid ablation. The detailed breakdown of the tests performed on the mothers' sera will be given later in section 3.2.

All thyrotoxic mothers after attending the first ultrasound examination were rescanned monthly until 36 weeks gestation to monitor fetal thyroid volume and fetal growth. If the maternal thyroid function was normal during all the scan periods, one value from each set of fetal data was selected to test the sensitivity of the nomogram established by this study. If the maternal thyroid function was abnormal, only the FTV at the time of abnormal maternal thyroid function was used. If the abnormal maternal thyroid function persisted for several scans, one value from each set of fetal data was selected to represent the whole.

2.2 Categorization of the Thyrotoxic Population

The subjects were divided into four groups according to maternal therapy and thyroid status during their attendance at the ultrasound examinations.

i. the treated group with normal maternal thyroid function

ii. the treated group with abnormal maternal thyroid function

iii. the untreated group with normal maternal thyroid function

iv. the untreated group with abnormal maternal thyroid function

The maternal thyroid status at the time of scan was determined retrospectively by retrieving the most recent result (with respect to the date of scan) of maternal thyroid function test on the hospital computer network system, LRR (Laboratory Result Report) System. Since the majority of the thyrotoxic mothers, irrespective of their current thyroid status, attended the Thyroid Clinic at a regular four-week interval until term with serum thyroid function test of TSH and/or T_4 performed on the same day of the clinic, the thyroid status would then be known for most scans. There was no more than 14 days between the date of thyroid function test and the date of scan.

The normal reference ranges for serum free T_4 (fT_4) by one-step immunoassays and sensitive TSH (sTSH) immunometric assays quoted in the Prince of Wales Hospital are 10.2 to 19.6 pmol/l and 0.3 to 4.0 mIU/l respectively. A sTSH value less than 0.03mIU/l is indicative of hyperthyroidism in the absence of pituitary disease. In pregnancy, these

values are debatable. Free thyroxine concentrations may be slightly lower compared to the non-pregnant range by the second trimester and may decrease further (by about 30% of its values in early pregnancy) by the third trimester. However, the changes in free thyroid hormone concentrations remain in the normal range (Yamamoto et al 1979, Parker JH 1985). A concomitant rise in the serum TSH levels has also been reported (Glinoer et al 1990).

In the treated mothers, the fT_4 levels were used to indicate the maternal thyroid status. If only sTSH had been obtained, the thyroid status was assigned as suggested by reference values.

In the untreated mothers[2], sTSH values were preferred to fT_4 level for initial diagnosis. If only fT_4 was available, the thyroid status was determined as suggested by reference values.

In both groups, the thyroid status for that scan would be assumed in accordance with the clinical condition if no recent maternal thyroid function was available (Table 4).

[2] The `untreated' mothers refer to those who were not currently treated with antithyroid drugs, therefore those who were on L-T_4 replacement were also included in this group.

Table 4. Determinating Tests for Maternal Thyroid Status

Thyrotoxic Population	Maternal Tests that may be available		
Treated	fT_4	sTSH	clinical
Untreated	sTSH	fT_4	clinical

**Tests with decreasing order of preference from right to left for determination of maternal thyroid status*

2.3 Intraobserver Error

The FTVs of thirty fetal thyroids were calculated by the measurements of the longest axes of the thyroid lobes. Every axis of the lobe was measured on the transverse and longitudinal images. The procedures were repeated three times on different images. The three sets of FTVs obtained from 30 fetal thyroids were then analysed by one-way ANOVA with equal sample sizes to determine the intraobserver variance.

2.4 Pilot Study

A pilot study was conducted on 40 normal fetal thyroids of 40 singleton pregnancies during December 94 and January 95 to determine which dimension of the fetal thyroid gland was the better estimate of the fetal thyroid size. The width, thickness, length and volume of both lobes of the fetal thyroid were recorded. The mean width, mean thickness, mean length by averaging the measurements of the two separate lobes, and the total thyroid volume were correlated with gestational age. The dimension that had the strongest correlation with gestational age as reflected by the corresponding coefficient of determination R^2 would then be taken as the sole measurement in this study.

2.5 Equipment

All the scans were performed using the high resolution 5MHz transducers of the following ultrasound equipment:

ATL HDI-3000

ATL Ultramark-9

Aloka SSD-2000

Aloka SSD-650

Philips SD-800

The electronic calipers of the five machines are calibrated monthly as quality assurance in order to ensure consistent and accurate measurements.

2.6 Measurements

i. Biparietal Diameter (BPD)

ii. Femur Length (FL)

iii. Abdominal Circumference (AC)

iv. The length of the separate thyroid lobes

v. The width of the separate thyroid lobes

vi. The thickness of the separate thyroid lobes

2.7 Growth Charts employed

The nomograms used for all the ultrasonic growth parameters: BPD, FL and AC were those established by the Hong Kong Tsan Yuk Hospital and in common use in Hong Kong (please see charts in appendix I).

2.8 Imaging Technique

2.8.1 BPD

The BPD was measured on an axial plane of the fetal head from outer to inner skull table. The intracranial landmarks include the falx cerebri anteriorly and posteriorly, the cavum septi pellucidi anteriorly and thalami in the midline, and the choroid plexus in the atrium of each lateral ventricle (Figure 1)(Hadlock FP 1994).

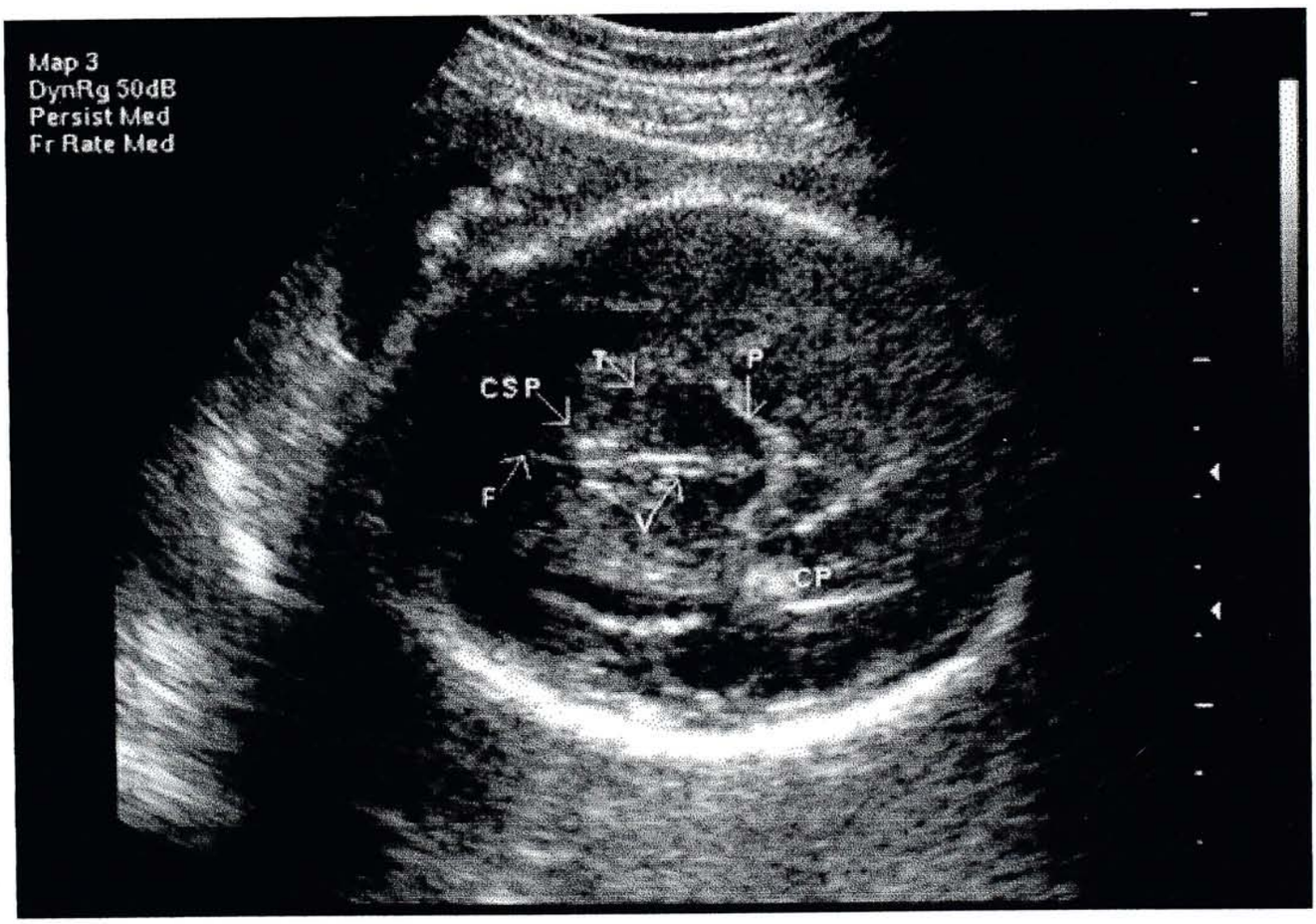

Figure 1. Axial plane of fetal head where BPD is measured. The landmarks should include the falx (F), the cavum septi pellucidi (CSP), thalami (T), the third ventricle (V), the cerebral peduncle (P) and the choroid plexus (CP) in the atrium of each lateral ventricle

2.8.2 FL

The measurement of the FL was made along the femur diaphysis and excluded the distal femoral epiphysis (Figure 2) (Hadlock FP 1994).

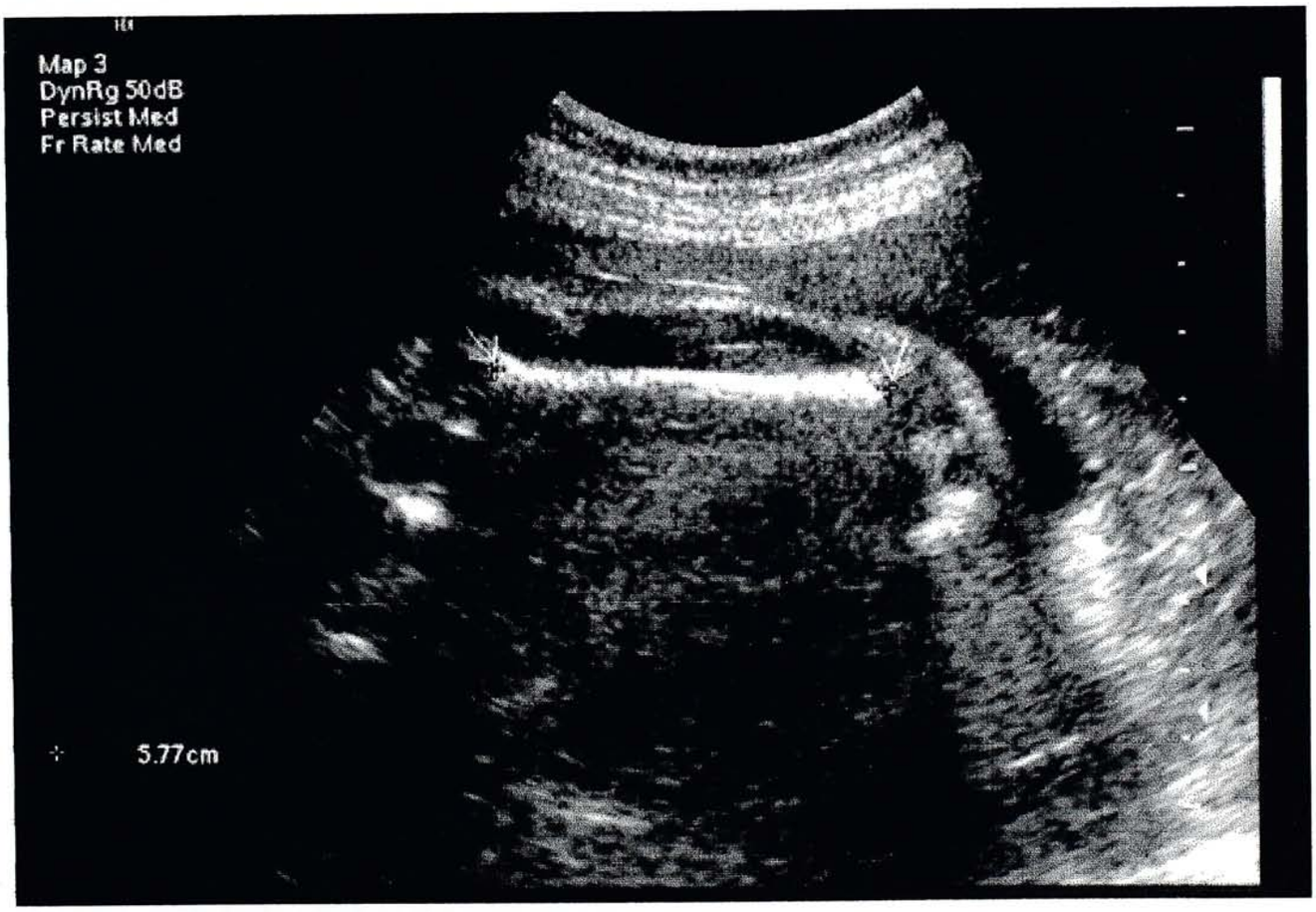

Figure 2. The longitudinal section of the fetal femur. The femur length is the distance between the two diaphyses as shown by the white arrows.

2.8.3 AC

The measurement of the AC was taken along the outer-to-outer margin of the axial plane of the fetal abdomen where the left portal vein enters deep in the liver with the stomach bubble appearing on the left upper quadrant (Figure 3) (Hadlock FP 1994).

Figure 3. The axial plane of the fetal abdomen where AC is measured. The arrow denotes the left portal vein in the fetal liver and a round stomach bubble appears on the left.

2.8.4 Linear Measurements of the Thyroid Lobes

The fetal thyroid gland was first identifed on the axial scan plane at the level of mid-neck as a bilobed homogeneous structure with the carotid arteries marking its outer margins (Figure 4a).

The maximum width and thickness of the gland were measured on the axial plane of a magnified image (Figure 4b). The favourable fetal position is when the fetus lies on its side with no neck flexion. Adequate liquor surrounding the fetal neck is an advantage.

The lengths of the separate lobes were obtained on the coronal plane of the fetal neck with trachea lying in between (Figure 5a & b).

The length of each axis was measured twice. The greater one was chosen to avoid underestimation as a result of misalignment during the scanning.

Figure 4a. Transverse section of fetal neck. The fetal thyroid is bordered on both sides by the carotid arteries (A) and jugular veins (V) with the trachea (curved arrow) lying in the midline. The measurements of the width (short white arrows) and thickness (long white arrows) of the separate lobes are demonstrated.

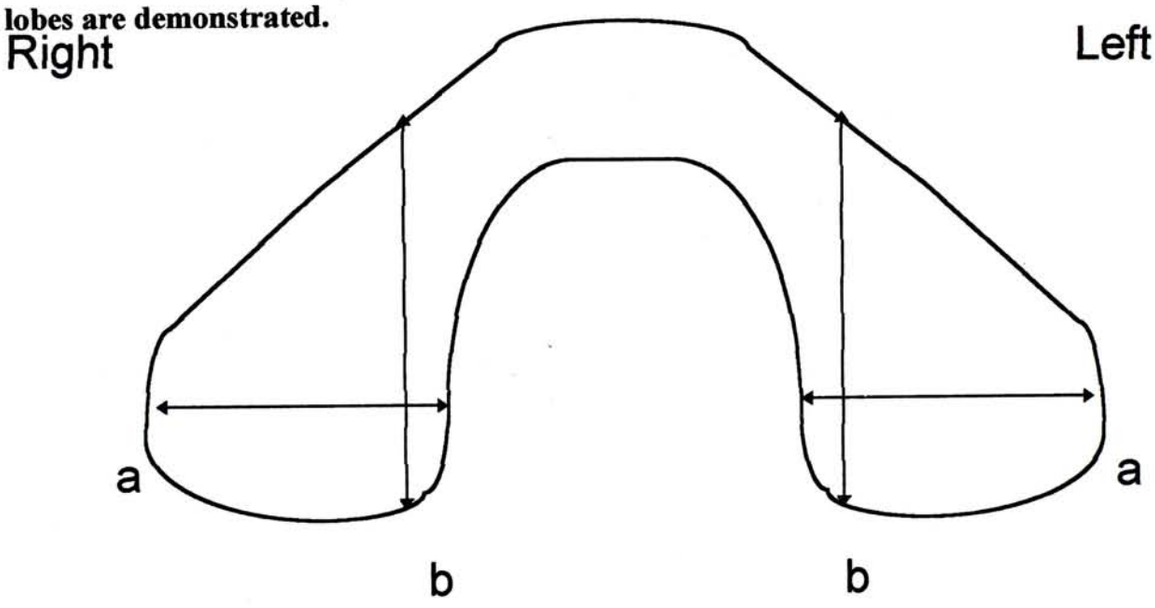

Figure 4b. The transverse section of the central portion of the normal thyroid gland where a,b represents the width and thickness of each lobe

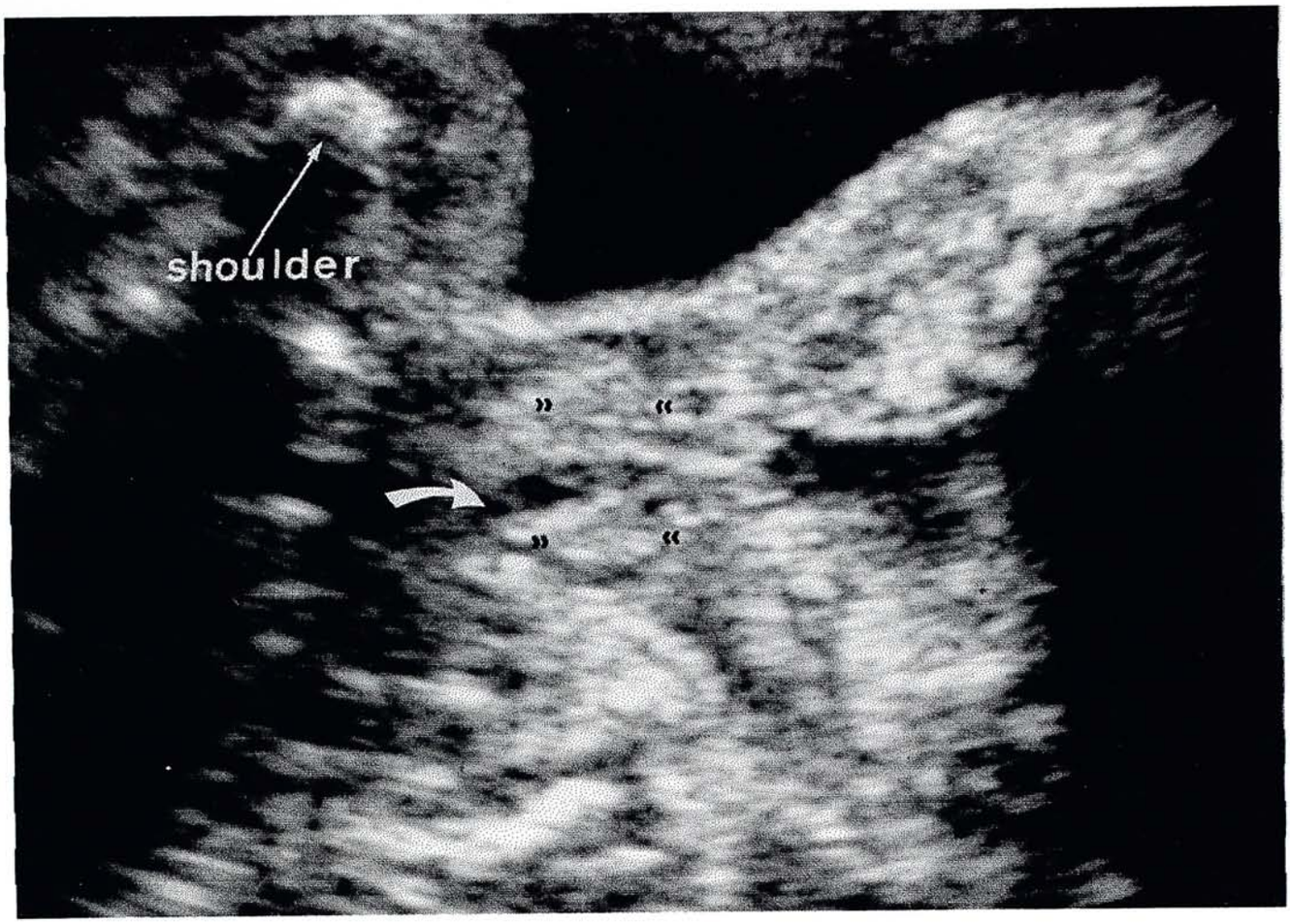

Figure 5a. Coronal section of the fetal neck. The measurement of the lengths of fetal thyroid lobes (double black arrowsheads) are shown.

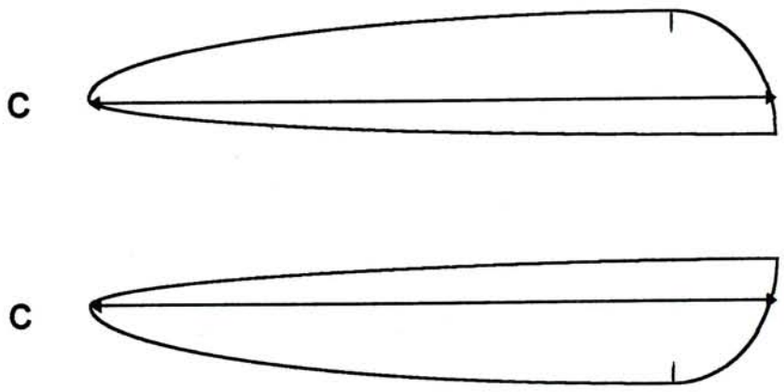

Figure 5b. The longitudinal section of the thyroid lobes where c represents the length of the long axis

2.9 Calculations

2.9.1 Fetal Thyroid Volume (FTV)

The FTV was estimated by the Ellipsoid Method with which the knowledge of the main axes of the thyroid lobes were required (Ueda 1990; Chanoine et al 1991). The FTV was calculated from the formula:

$FTV = V_{right\ lobe} + V_{left\ lobe} + V_{isthmus}$ where

the partial volume of each lobe $V = \pi/6\ (a \times b \times c)$ and

a, b, c represents the maximum width, thickness and length of each lobe.

the volume of the isthmus $V_{isthmus} = 0.05\ (V_{right\ lobe} + V_{left\ lobe})$

2.9.2 Estimated Fetal Weight (EFW)

The estimated fetal weight was estimated by the equation utilizing the three growth parameters BPD, FL, and AC (Hadlock et al 1985):

$$EFW = Log_{10}(\text{birth weight})$$

$$= 1.335 - 0.0034(AC.FL) + 0.0316(BPD) - 0.0457(AC) + 0.1623(FL)$$

2.9.3 Fetal Thyroid Growth Rate

Fetal thyroid growth rate was calculated by the regression equation of FTV versus gestational age. It was the difference of FTVs at a particular interval of gestation divided by the corresponding period of gestation.

2.9.4 Fetal Thyroid Volume to Estimated Fetal Weight Ratio(V/W)

The ratio was obtained by dividing the FTV of a fetus with its concurrent EFW .

2.10 Gestational Age of the Fetus

2.10.1 Normal Population

The gestational age of the fetus in the normal population was determined by averaging the sonographic ages of three growth parameters (BPD, FL, and AC), irrespective of the menstrual age. Those in whom the difference between BPD, FL and AC was more than seven days were excluded.

2.10.2 Thyrotoxic Population

For the first scan, the gestational age of the fetus in the thyrotoxic population was assigned by averaging the sonographic ages of three growth parameters similar to the normal population but ignoring the discrepancy of sonographic age between individual growth parameters. The rationale being that use of the menstrual age to predict the gestational age of the fetus cannot be relied upon as menstrual irregularity and anovulation occur commonly in mothers with Graves' disease (Goldsmith et al 1952; Thomas & Reid 1987). Discrepancy between individual growth parameters was ignored because intrauterine growth retardation is a common reported complication of the fetuses of thyrotoxic mothers (Becks and Burrow 1991; Seely and Burrow 1994), and a small AC is frequent.

For subsequent scans, the gestational age of the fetus was determined by adding the respective time interval to the gestational age of the previous scan.

2.11 Analytical Methods

2.11.1 Bivariate regression was used to evaluate the relationships between FTV and the independant variables BPD, FL, AC, gestational age and EFW.

2.11.2 Multiple regression was employed to analyse more than one independent variables: GA and EFW simultaneously, in order to determine which variable had the strongest relationship with FTV.

2.11.3 Plots of the residuals, as a diagnostic of homoscedasticity and normality of data, were checked for every regression line of best fit on the scattergrams. Transformation of data was performed if the assumptions of normality and homoscedasticity did not hold. Nomogram of FTVs was produced by the predicted mean $\pm$ 1.96SD obtained by the regression equation. The *standard deviation from regression(SD)* or *the standard error of the estimate* is equal to the square root of the residual mean square. (Daly et al 1991; Triola 1994).

2.11.4 The independent t-test was utilized to compare the means of V/W ratios of two independent samples: normal versus thyrotoxic population, normal versus thyrotoxic treated group, and normal versus thyrotoxic untreated group.

2.11.5 One-way ANOVA with equal sample sizes was used to determine the proportion of variance attributable to intraobserver differences.

2.11.6 One-way ANOVA with unequal sample sizes was used to compare the means of V/W ratios in different age subgroups.

2.11.7 The Z scores (the number of standard deviations that a given value is above or below the mean) of V/W ratios in the treated and untreated groups of the thyrotoxic population were calculated and compared with the F- test (two sample for variance).

2.11.8 Wilcoxon rank sum (Mann-Whitney U or Kendall's S) test was applied to check if there was significant difference of the FTVs in the treated and untreated mothers of the thyrotoxic population.

2.11.9 The null hypothesis was the absence of correlation or difference between the variables considered. The probability value taken to indicate statistical significance was $\rho = 0.05$. Hypothesis was rejected if ρ was < 0.05. All the statistical analyses were performed using computer software Microsoft Excel (version 5) and Statistical Package for the Social Sciences (SPSS release 6).

Chapter 3 Results

A total of 289 fetal thyroids from the normal population and 72 fetal thyroids (184 measurements) from the at-risk (thyrotoxic) population were measured between 20 and 36 weeks of gestation. The mean age was 27.6 weeks for the fetuses in the normal population and 28.4 weeks for those in the thyrotoxic population. The normal mean FTV and its relationships with different growth parameters, rate of normal fetal thyroid growth, and mean V/W ratio were established and compared with the thyrotoxic population.

3.1 Intraobserver Error

The three sets of FTV measurements of the thirty fetal thyroids were compared with one-way ANOVA and found that there was no significant difference between the three sets of data. The intraobserver error was hence negligible.

3.2 Pilot Study

Forty fetal thyroids of the normal population were included in the pilot study. It was shown that FTV had the strongest correlation with gestational age reflected by the highest R^2 (0.742) compared to all the other linear thyroid dimensions (Figure 6-9). Among the three linear dimensions, the mean transverse diameter (R^2 = 0.6861) is the best and the mean longitudinal length (R^2 = 0.5555) is the worst to reflect thyroid size.

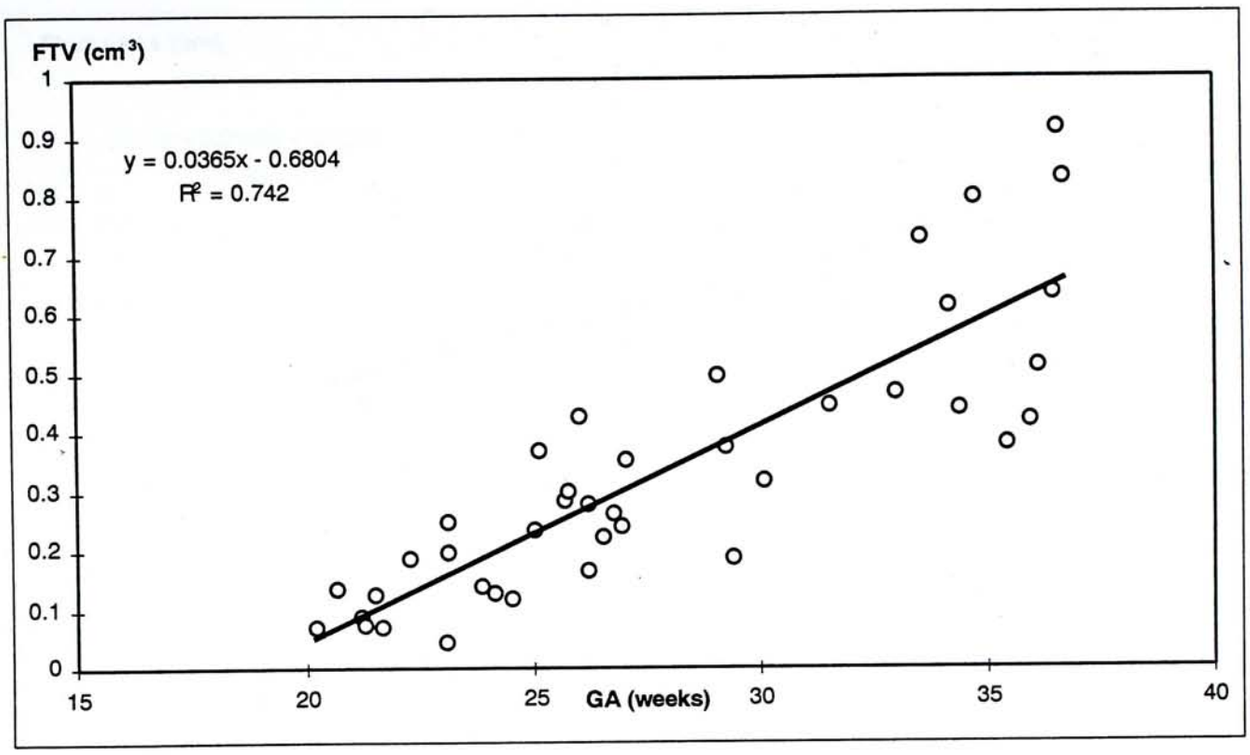

Figure 6. Scattergram of FTV versus GA

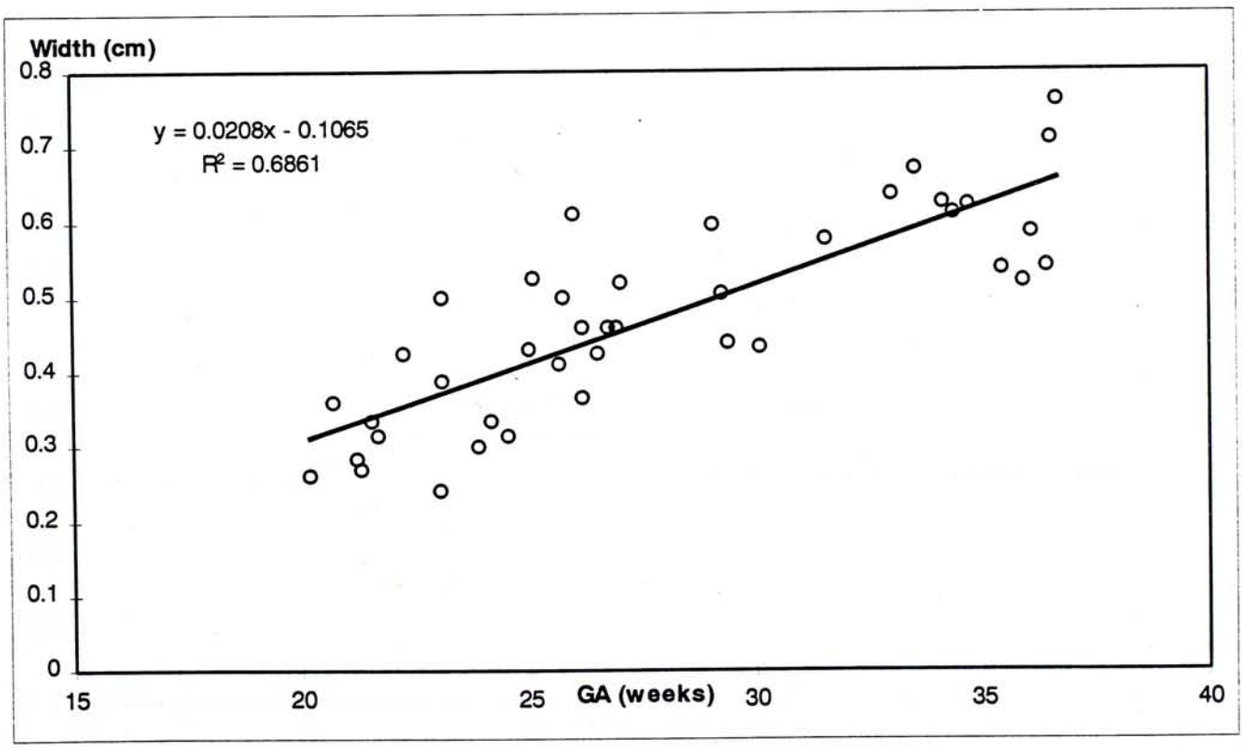

Figure 7. Scattergram of mean width of the thyroid lobes versus GA

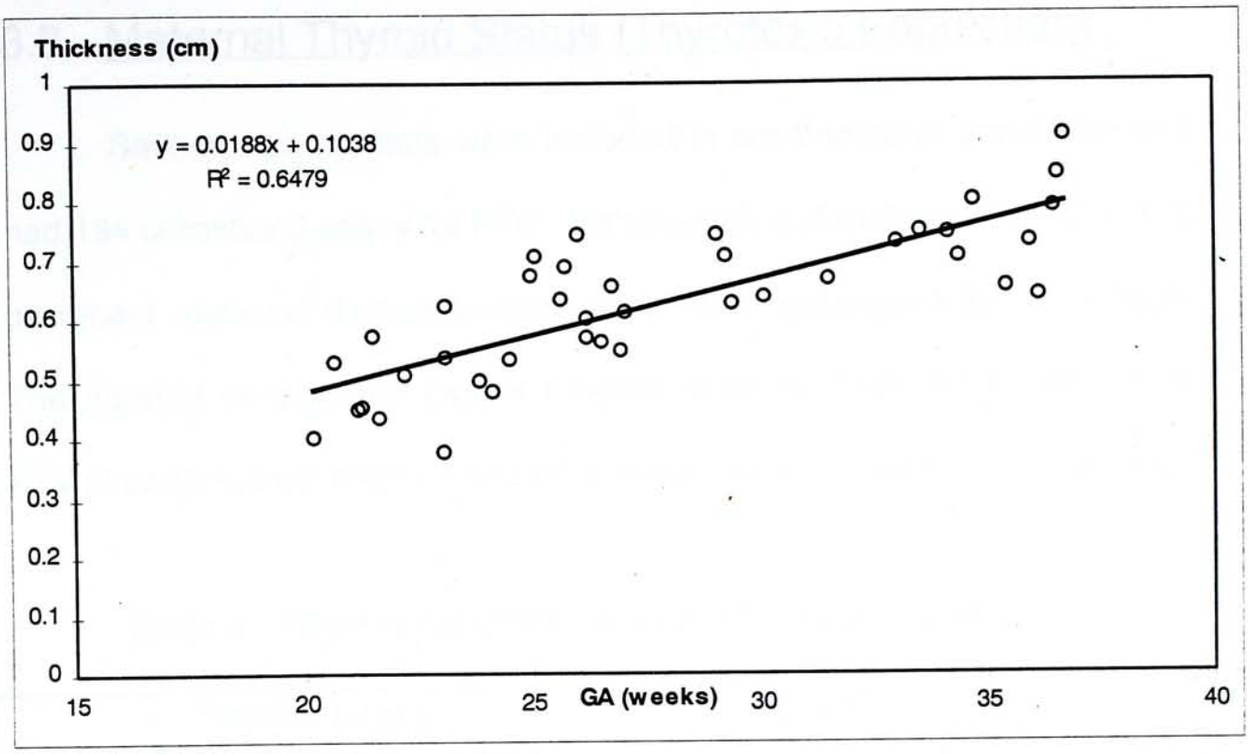

Figure 8. Scattergram of the mean thickness of thyroid lobes versus GA

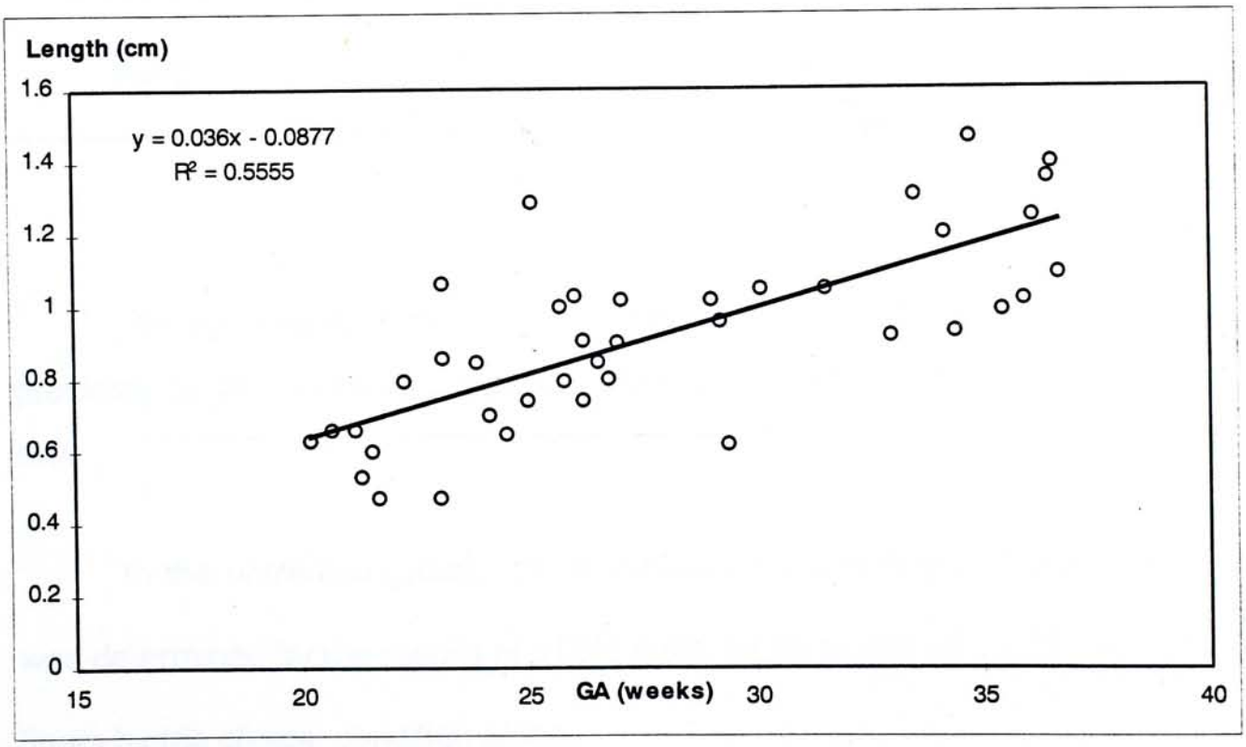

Figure 9. Scattergram of the mean length of thyroid lobes versus GA

3.3 Maternal Thyroid Status (Thyrotoxic Population)

Seventy-two mothers were included in our thyrotoxic population and had 184 ultrasound scans for FTV. Determination of maternal thyroid status by recent maternal thyroid function tests[3] was undertaken for each scan. The number of maternal thyroid function tests available for correlation of FTV at each scan in the treated and untreated groups was listed in Table 5.

Table 5. Thyroid Function Tests in 72 Thyrotoxic Mothers

Treated Group (34 mothers with 91 scans)		**Untreated Group (38 mothers with 93 scans)**	
Tests Done	No. of Scans	Tests Done	No. of Scans
fT_4 only	57	fT_4 only	30
fT_4 + sTSH	33	fT_4 + sTSH	30
sTSH only	0	sTSH only	10
none	1	none	23

In the treated group, all the mothers, but one, had fT_4 tests in proximity to the ultrasound scans. Thirty-three had, in addition an sTSH test.

In the untreated group, on 40 occasions the maternal thyroid status was determined by the results of sTSH tests; on 30 occasions by fT_4; and 23 times by the clinical condition alone.

[3] Recent maternal thyroid function test means test is available or has been done within 14 days prior to or following that scan.

3.4 Fetal Thyroid Volume (FTV)

3.4.1 Normal Population

The normal fetal thyroid gland could be confidently identified and measured by ultrasound at around 20 weeks of gestation as a tiny homogeneous bilobulated glandular structure lying in the mid-neck straddling the trachea and bounded by the carotid arteries laterally. The success rate of measuring FTV during the period of gestation from 20 to 36 weeks was over 90% and then fell toward late gestation. It was found that the mean ($\pm$SD) FTV was 0.23 $\pm$ 0.18cm^3 (range: 0.022cm^3 - 0.85cm^3; median 0.17cm^3) between 20 and 36 weeks of gestation. The FTV demonstrated a positive correlation with gestational age in an exponential fashion. The respective regression equation at different gestational age was $y = 0.0035e^{0.1399x}$ where y denoted the FTV and x denoted the gestational age (Figure 10).

Although the regression was better represented by the log(FTV) (Figure 11), the scattergram on the linear scale with a curvilinear regression line was easier to use in clinical practice. The nomogram for FTV was produced using the predicted mean $\pm$ 1.96SD from the regression equation (Figure 12).

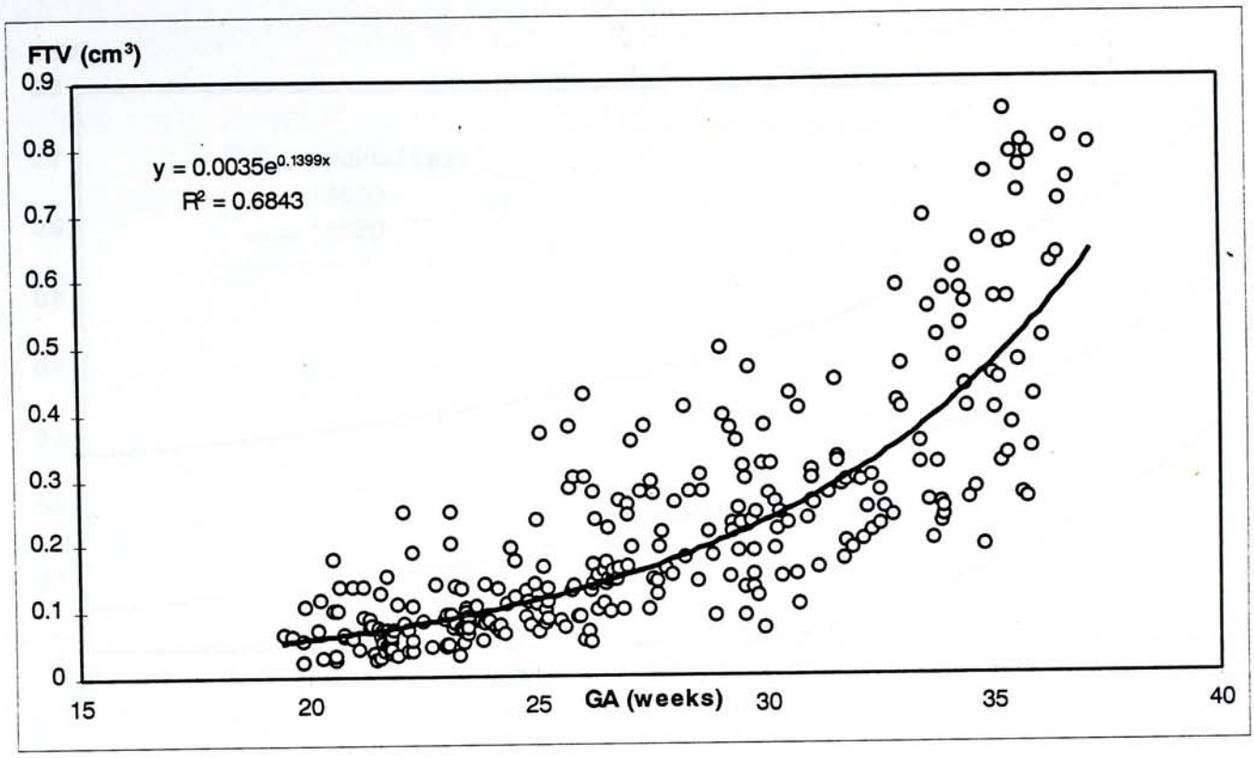

Figure 10. Relationship of FTV with GA

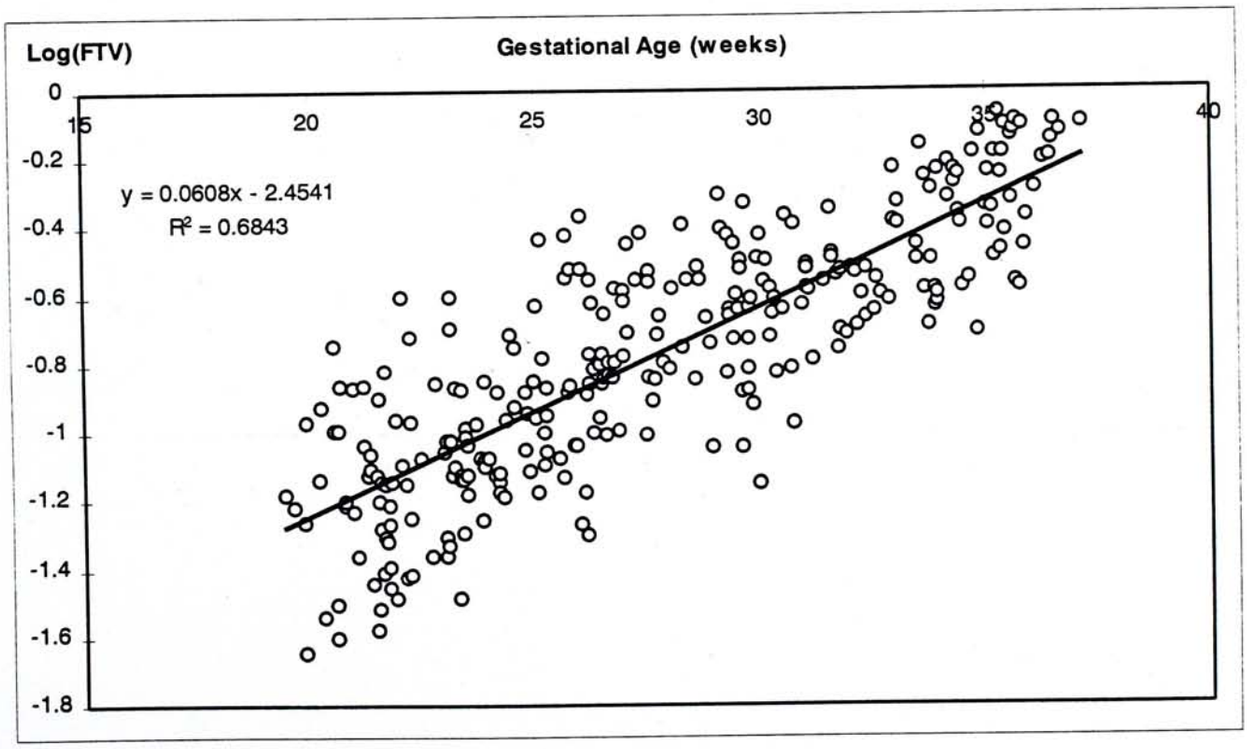

Figure 11. Relationship of log(FTV) with GA

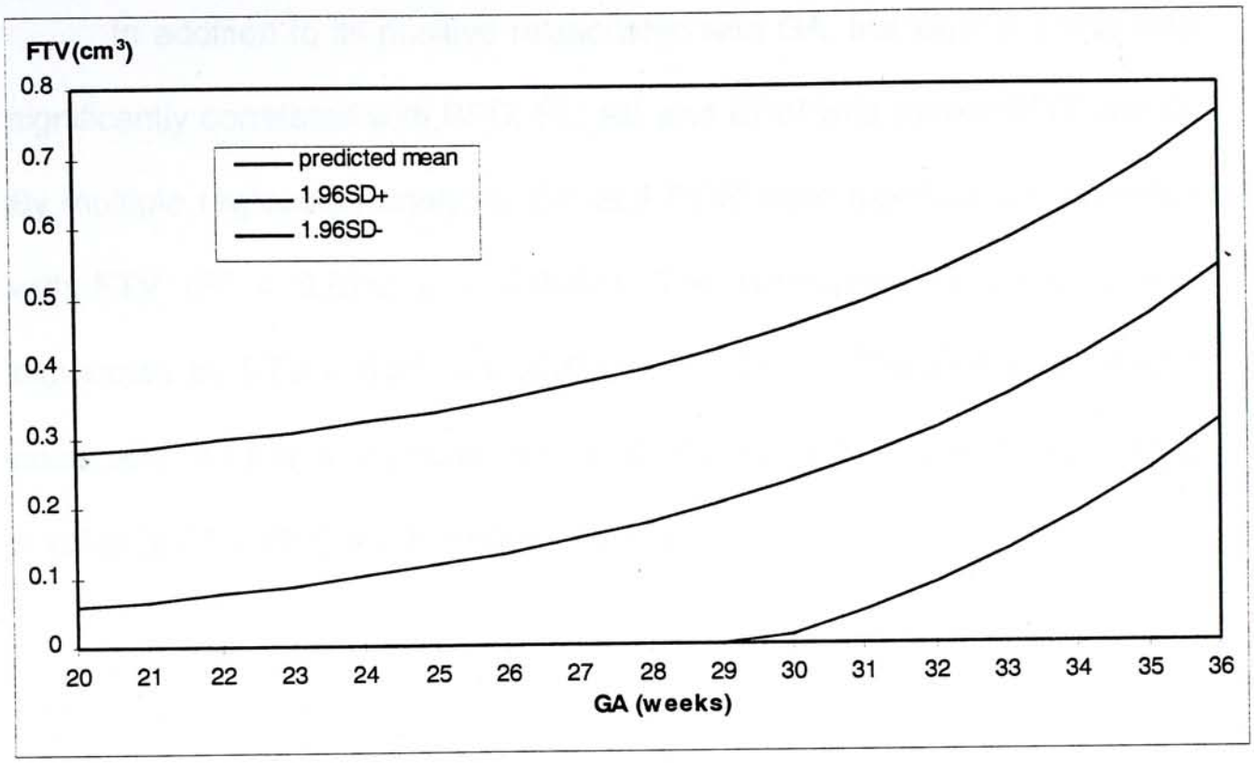

Figure 12. Nomogram of FTV

In addition to its positive relationship with GA, the log(FTV) was also significantly correlated with BPD, FL, AC and EFW with similar R^2 (Table 6). By multiple regression analysis, GA and EFW were significantly correlated with FTV (R^2 = 0.674; $\rho < 0.0001$). The corresponding equation was expressed by FTV = 0.38 - 0.02(GA) + 0.3(EFW). The partial correlation coefficient of EFW was greater than that of GA (0.365 versus -0.156) with a ρ value (2.27×10^{-70}) much smaller than 0.05 .

Table 6. Relationship between the log(FTV) and different independent parameters (n = 289)

Parameters	R^2	ρ
GA	0.6843	6.48×10^{-63}
BPD	0.6773	4.25×10^{-57}
AC	0.6742	1.63×10^{-60}
FL	0.6710	1.3×10^{-56}
EFW	0.6638	2.56×10^{-70}

3.4.2 At-risk Group

Seventy-two fetal thyroids were measured from 184 scans in the at-risk group during the period from September 1995 to March 1997. The FTVs related to different group of maternal thyroid status and therapy were plotted against the nomogram (Figure 13-19) and their distribution was shown in Table 7.

Table 7. Distribution of Cases between the Groups

Groups	Number of cases
Treated euthyroid	24
Treated (hyperthyroid / hypothyroid)	10
Treated (PTU)	27
Treated (CMZ)	7
Untreated euthyroid	25
Untreated (hyperthyroid / hypothyroid)	8
Untreated (on L-T_4 replacement)	5

Treated Group There were altogether thirty-four fetal thyroids (twenty-four in the euthyroid, five each in the hyperthyroid and hypothyroid mothers) studied in the treated group who had currently received antithyroid treatment before the ultrasound scan. We found that the FTVs in these two groups with normal and abnormal maternal thyroid function were all within normal range and showed a constant trend around the mean irrespective of the maternal thyroid status (Figure 13 & 14).

The distribution of FTVs in the mothers on PTU and CMZ was compared and did not appear to differ much from each other. Both groups showed little variation around the mean (Figure 15 &16) and absence of statistical significant difference.

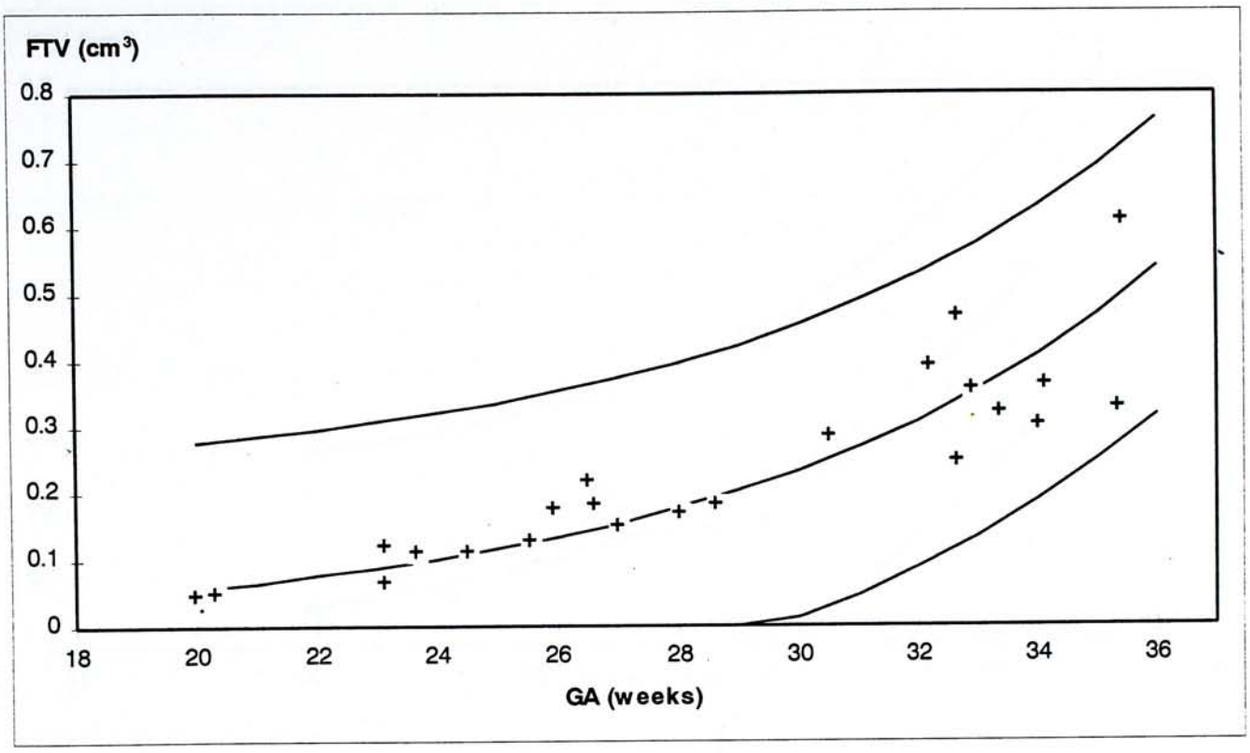

Figure 13. The distribution of FTVs in the treated euthyroid mothers (n=24)

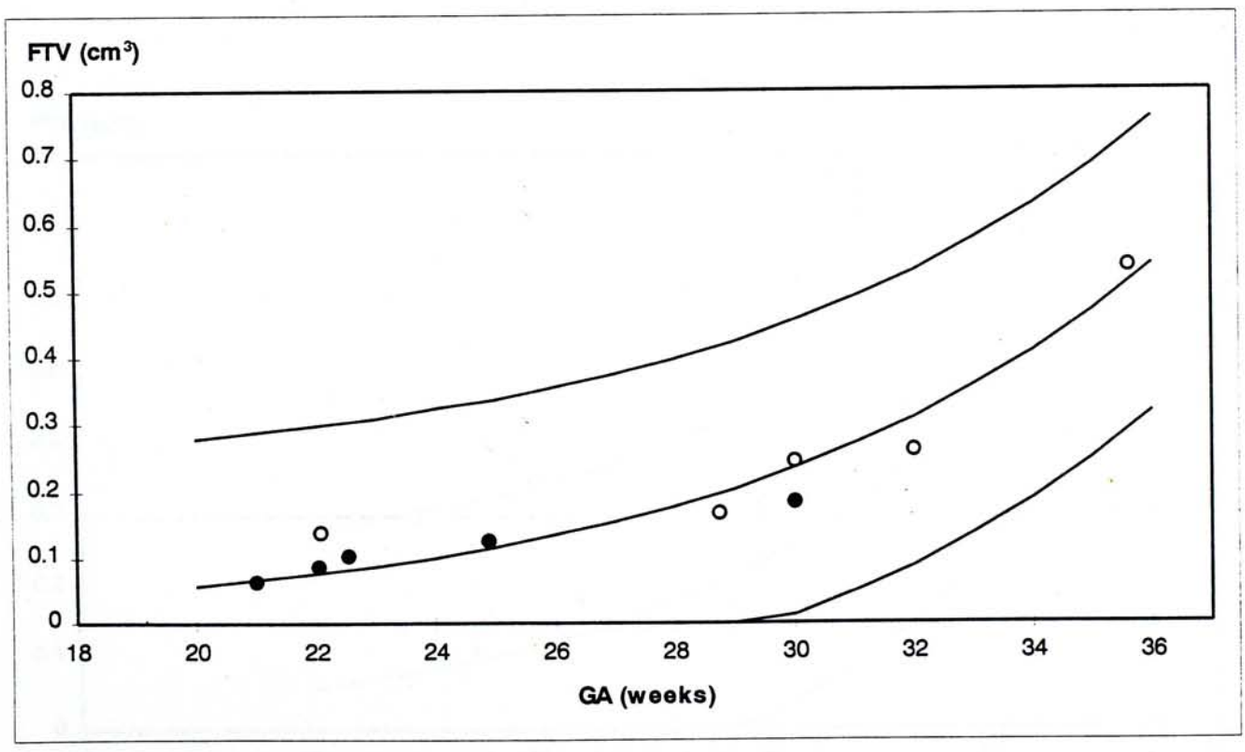

Figure 14. The distribution of FTVs in the treated mothers (n= 10) where (•) and (○) represent the FTVs in the hyperthyroid and hypothyroid mothers respectively

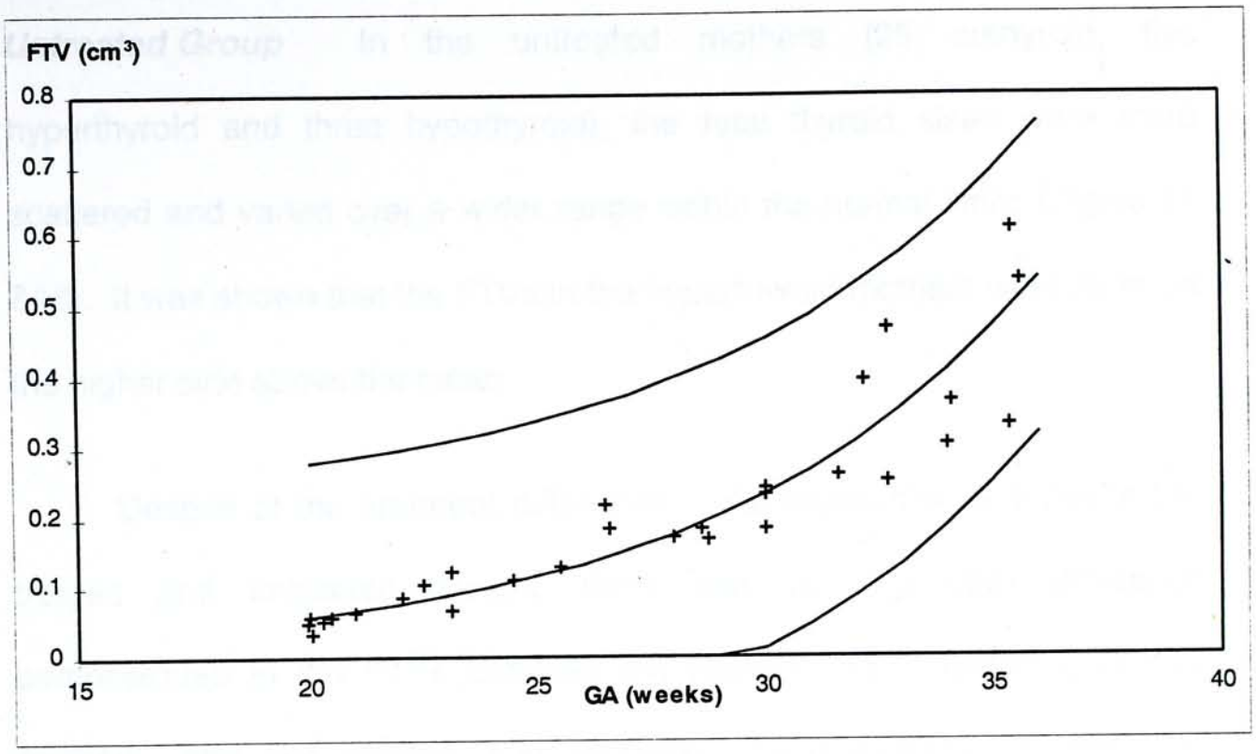

Figure 15. The distribution of FTVs in the treated mothers on PTU (n=27)

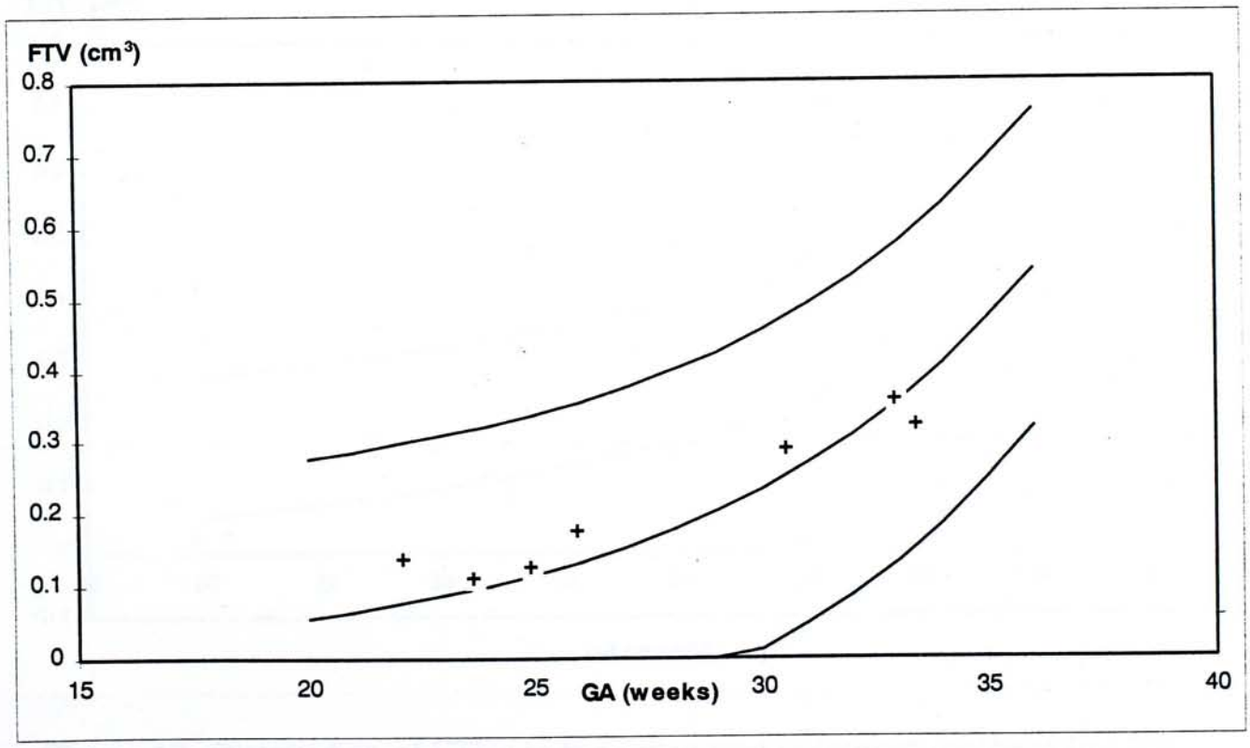

Figure 16. The distribution of FTVs in the treated mothers on CMZ (n=7)

Untreated Group In the untreated mothers (25 euthyroid, five hyperthyroid and three hypothyroid), the fetal thyroid sizes were more scattered and varied over a wider range within the normal limits (Figure 17 &18). It was shown that the FTVs in the hyperthyroid mothers were more on the higher side above the mean.

Despite of the apparent difference in the distribution of FTVs in the treated and untreated groups, there was no significant difference demonstrated in the FTVs between the treated and untreated euthyroid mothers, and the treated and untreated hyper-/hypothyroid mothers. Further, the size of fetal thyroids in the mothers (n=5) who were on L-T_4 replacement was shown in Figure 19.

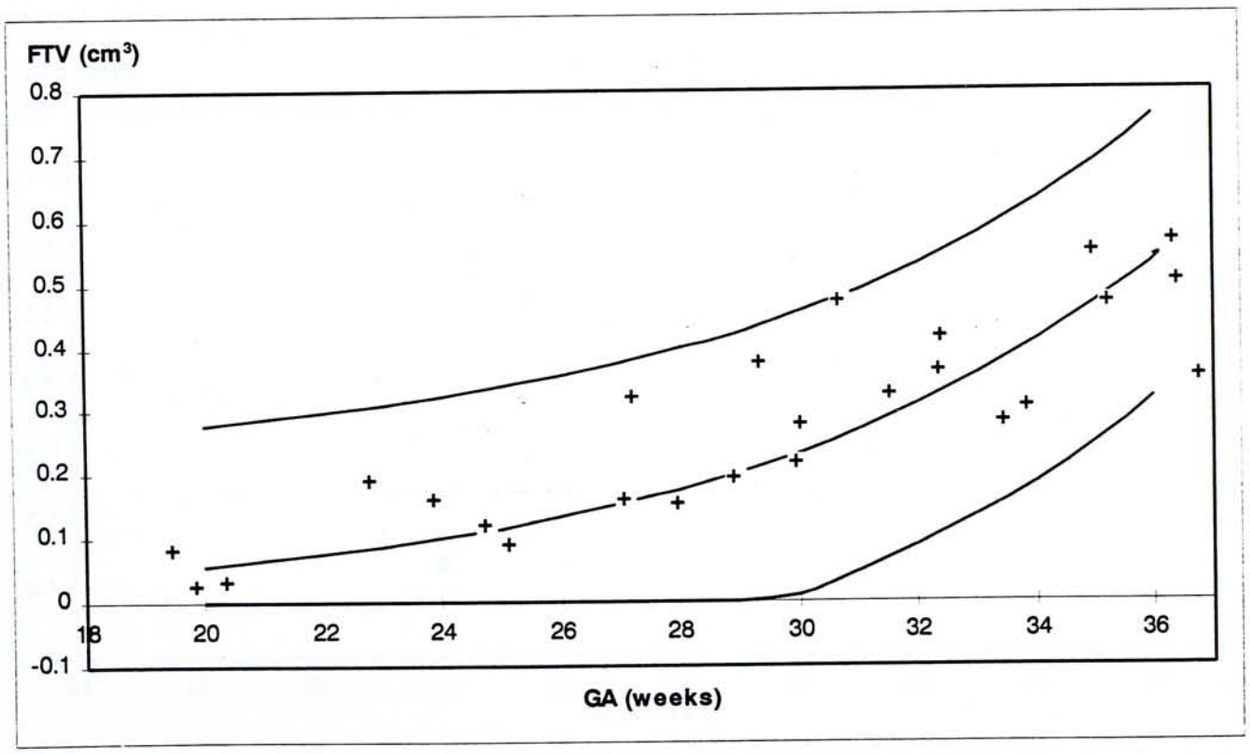

Figure 17. Distribution of FTVs in the untreated euthyroid mothers (n= 25)

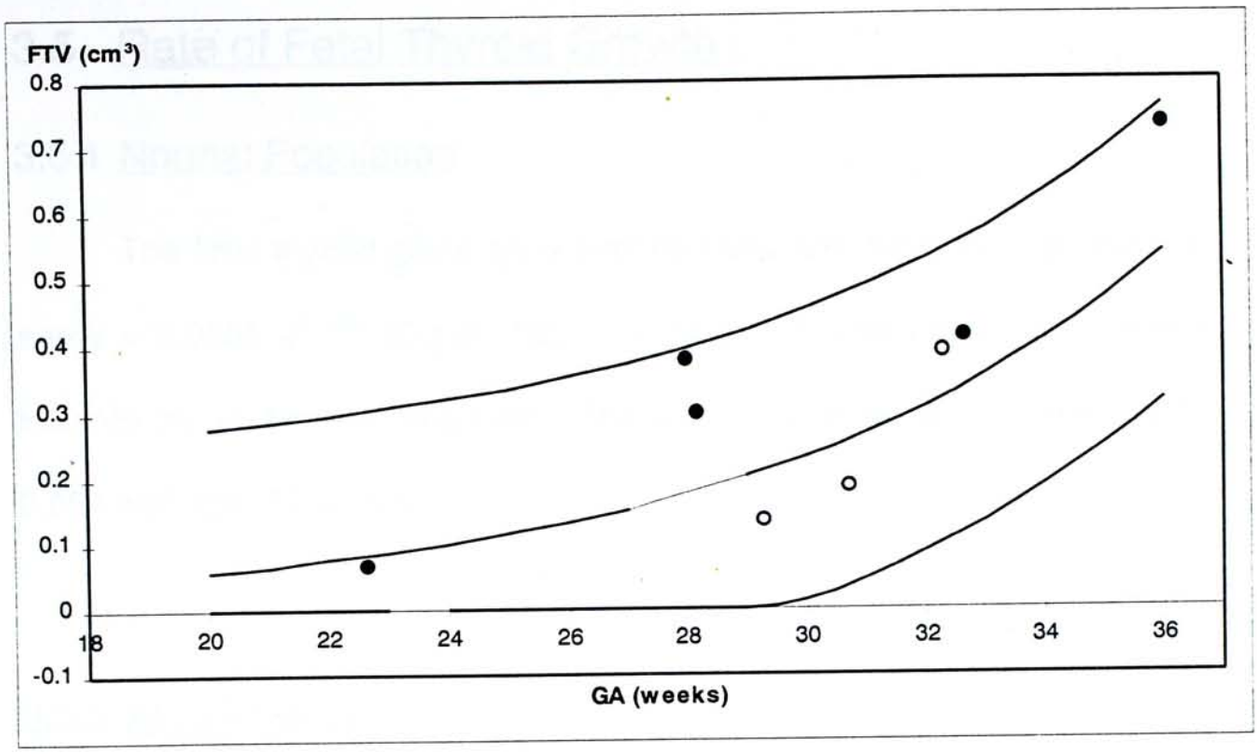

Figure 18. Distribution of FTVs in the untreated mothers (n=8) where (•) and (○) represent the FTVs in the hyperthyroid and hypothyroid mothers respectively

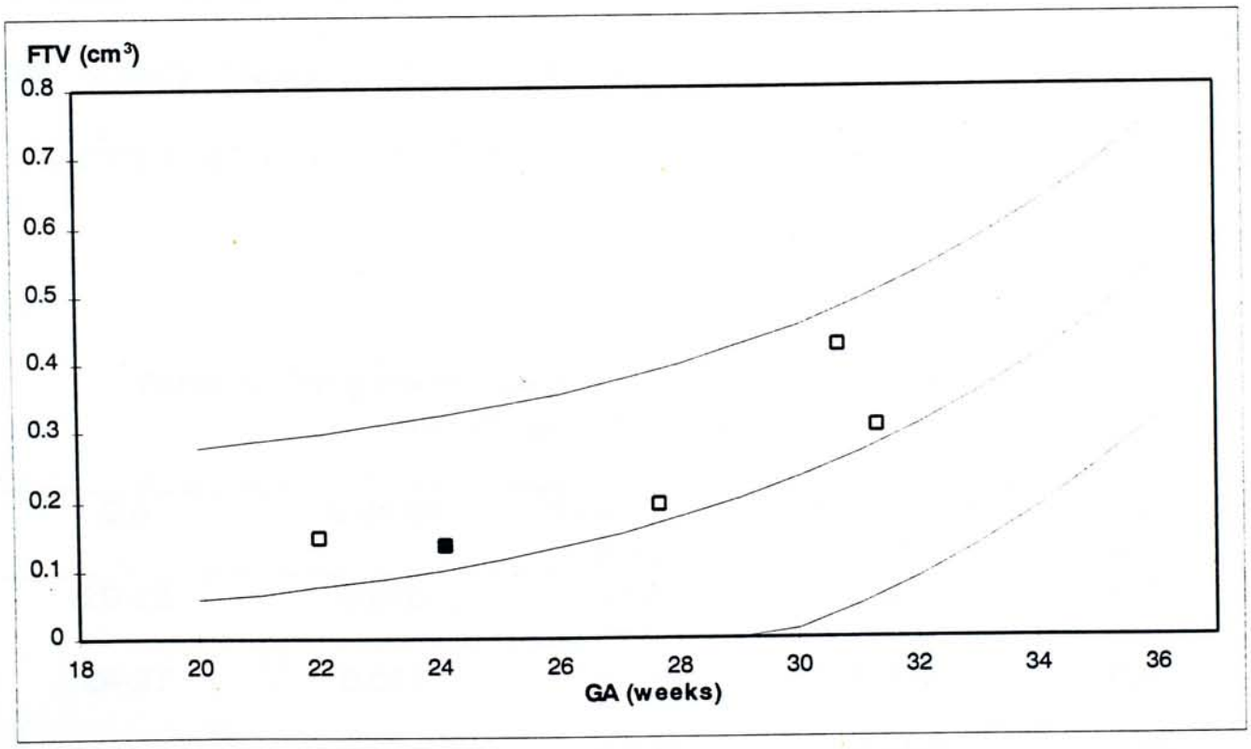

Figure 19. The distribution of FTVs in the mothers on L-T_4 replacement where (■) and (□) represent the FTVs in the hyperthyroid and euthyroid mothers respectively

3.5 Rate of Fetal Thyroid Growth

3.5.1 Normal Population

The fetal thyroid gland grew exponentially with advancing gestational age $y = 0.0035\ e^{0.1399x}$ (Figure 10). The rate of thyroid growth was fastest towards the end of the pregnancy. The weekly increase was approximately 0.054 cm^3 after 32 weeks.

3.5.2 At-risk Group

The growth rate of the fetal thyroids in the thyrotoxic group was similar to that of the normal population. The weekly increase was 0.052 cm^3 after 32 weeks by the regression equation $0.0046\ e^{0.1323x}$. Subdividing the thyrotoxic group into the treated and untreated subgroups demonstated that the weekly increase at the corresponding period of gestation was respectively 0.051 cm^3 and 0.055 cm^3 (Table 8).

Table 8. The growth rate (cm^3/week) of FTV in the normal and thyrotoxic population

GA	Normal	Thyrotoxic (total)	Thyrotoxic (treated)	Thyrotoxic (untreated)
20-23	0.010	0.011	0.010	0.011
24-27	0.017	0.018	0.017	0.019
28-31	0.031	0.030	0.030	0.032
32-35	0.054	0.052	0.051	0.055

3.6 Fetal Thyroid Volume to Estimated Fetal Weight (V/W) Ratios

3.6.1 Normal Population

The mean V/W ratio (± SD) in the normal fetuses was relatively constant equal to 0.163 ± 0.079 cm^3/kg. By one way ANOVA analysis, there was no significant difference demonstrated between each age subgroup ($\rho > 0.05$) (Table 9).

However, the mean value of V/W ratio under 36 weeks (0.161 ± 0.080 cm^3/kg) was significantly smaller than that over 36 weeks (0.200 ± 0.061 cm^3/kg).

Table 9. The V/W ratios in the Normal Population

GA	V/W ratios **0.163 ± 0.079 cm^3/kg**
20-23	0.165 ± 0.100
24-27	0.161 ± 0.086
28-31	0.154 ± 0.064
32-35	0.161 ± 0.059
≥36	0.200 ± 0.061

3.6.2 At-risk Group

The overall mean V/W ratio (± SD) was 0.170 ± 0.055 cm^3/kg. This is higher than the overall mean for the normal population (but not statistically significant). As the at-risk group is heterogeneous, they were divided into the treated and untreated groups.

The treated group had a V/W ratio of 0.159 ± 0.039 cm^3/kg. This is smaller than the normal group but again this difference was not statistically significant.

The untreated at-risk group however had a noticeably larger V/W ratio of 0.180 ± 0.065 cm^3/kg. This was larger than the normal population and the treated population, but once again the significance of this group against the normals did not reach statistically acceptable levels.

However, the range of z scores of the V/W ratios was narrower and the values smaller in the treated (ranged from -0.72 to 1.24) than in the untreated group (ranged from -1.11 to 1.93) (Figure 20 & 21). There was significant difference between the two groups ($\rho = 0.0016$)

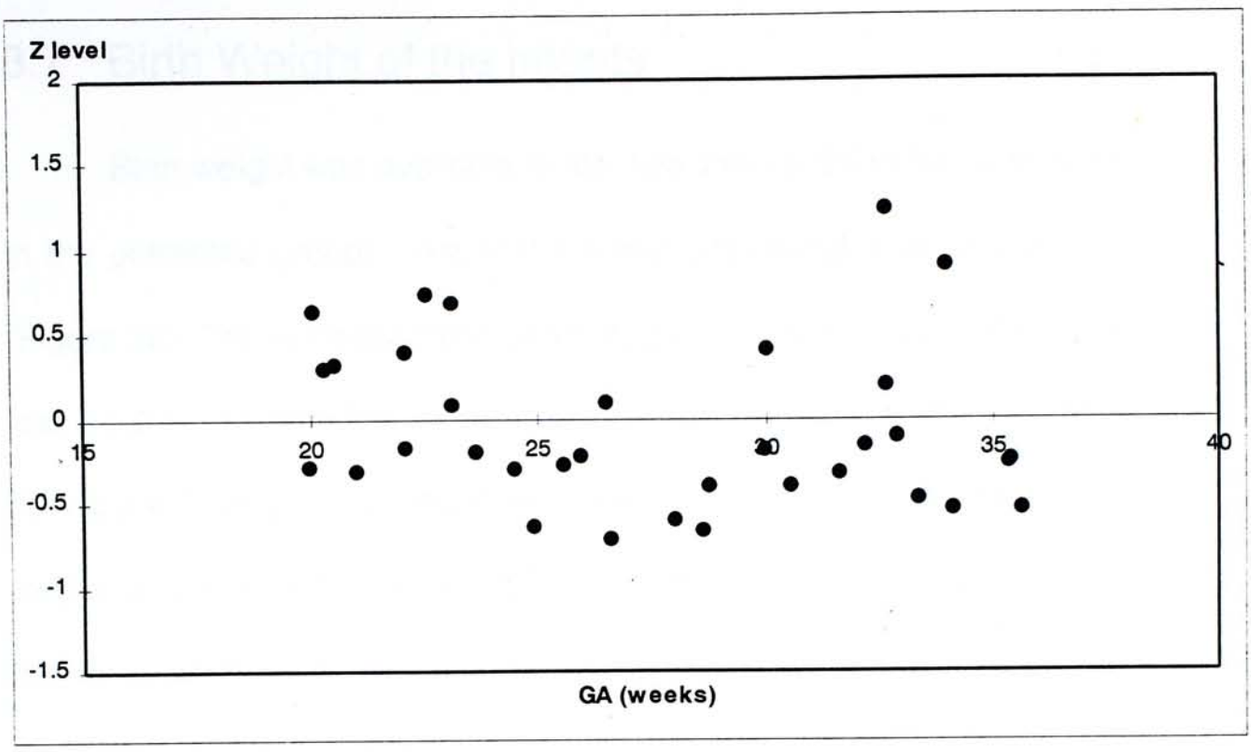

Figure 20. The Z-level of the V/W Ratios in the Treated Group

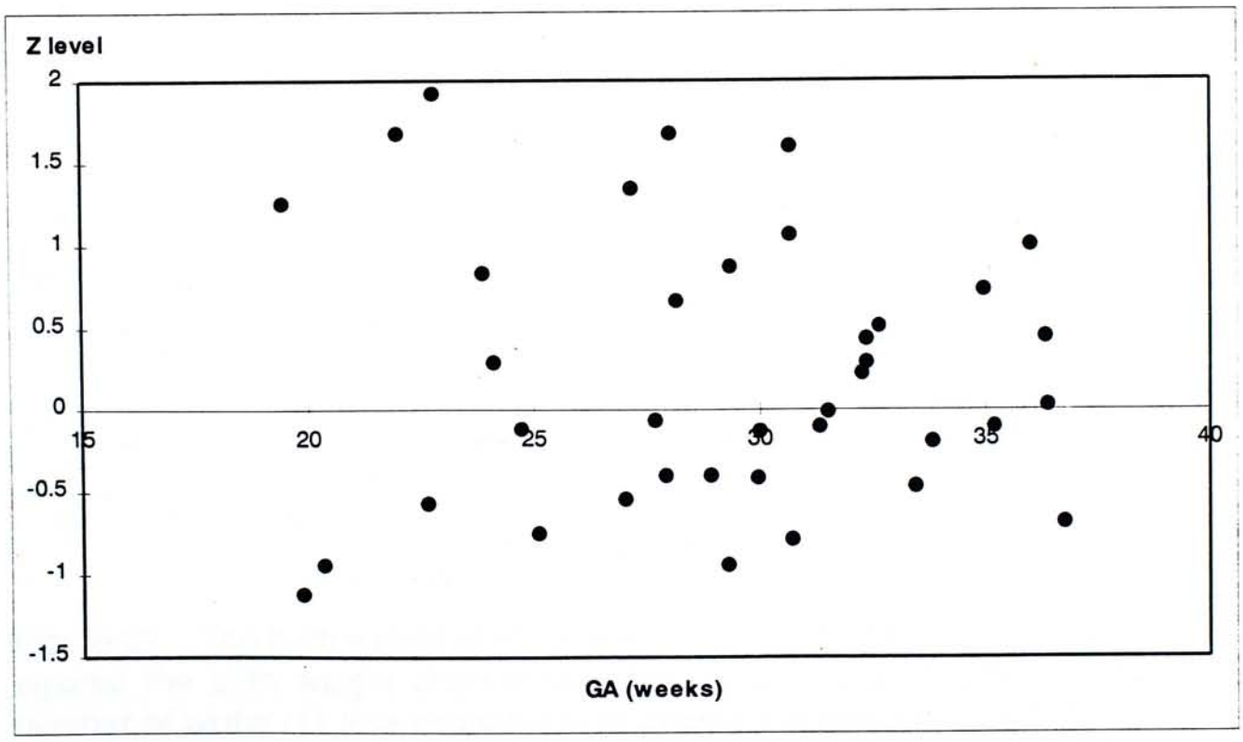

Figure 21. The Z-level of the V/W Ratios in the Untreated Group

3.7 Birth Weight of the Infants

Birth weight was available in fifty-two infants (28 in the treated and 24 in the untreated group). Six of them had birth weights at or below 2.5 kg (Figure 22). The corresponding percentage of low birth weight (LBW) infants was 11.5%. Five of the six infants' mothers were on antithyroid treatment during pregnancy. There were two babies born prior to 37 weeks, one at 34 weeks and one at 35 weeks, equivalent to 3.8% of prematurity. All eight mothers, apart from Graves' disease, had no known history of anemia, diabetes, cardiac, respiratory, liver nor renal disease.

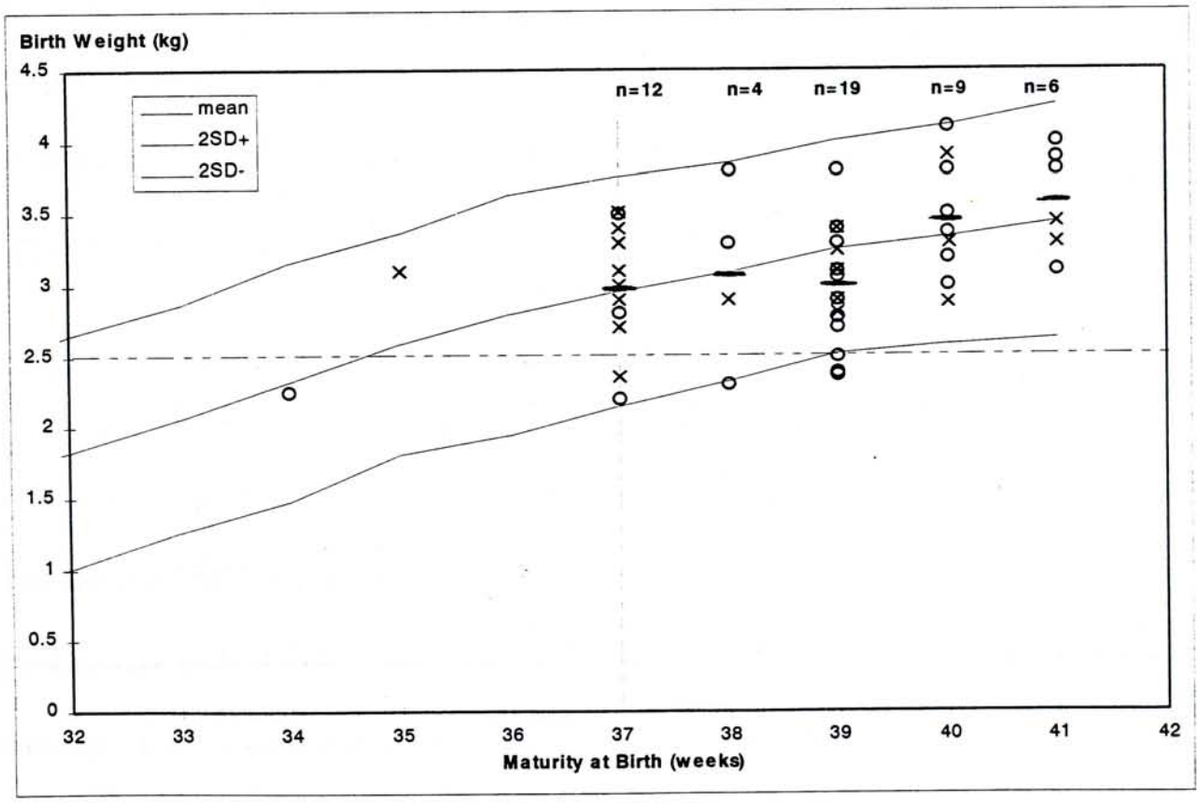

Figure 22. The birth weight of 52 infants in this thyrotoxic population plotted against the birth weight chart established by the data obtained from the number of births (11,258 neonates with gestational age from week 32 to 41 in year 95 and 96) at the Prince of Wales Hospital where (o) denotes the infants of the treated mothers and (x) denotes the infants of the untreated mothers.(-) represents the mean birthweight of the infants in the thyrotoxic population at a particular gestational age.

Chapter 4 Discussion

4.1 Methodology

4.1.1 Volume Measurement - method of choice

In adults, thyroid size measurement is important in the assessment and management of thyroid disease. The thyroid size can be determined by palpation, scintigraphy and ultrasonography. Thyroid palpation is a risk-free and simple procedure for initial clinical assessment, but skilful palpation of the thyroid gland takes practice (Kaplan 1985). A previous study on adults in this department showed that clinical palpation of small thyroids overestimated their volume by an average factor of almost two (Tsao et al 1988). This suggests that clinical estimation of thyroid volume by palpation is likely to be even more inaccurate in neonates and of course cannot be applied to the in-utero `patient'.

Scintigraphy had long been accepted for estimation of thyroid size which was based on the ellipsoid model, the calculated value was used to decide the therapeutic dose of radioactive iodine administered to the patient (O'Connor et al 1979; Krasznai et al 1985). This method is inapplicable to fetuses due to its radiation hazard and technical difficulty. Ultrasonography hence remains the sole method of choice.

Thyroid size can be reflected by the linear measurements of the thyroid gland such as the maximum length of each axis or directly by its

volume. The pilot study of 40 fetal glands found that volume measurement correlated best with gestational age as it carried the highest coefficient of determination, R^2. The value was 0.742 for volume measurement while the R^2 for the other linear dimensions were below 0.7.

Although the nomograms of transverse width and circumference of the fetal thyroid have been established in 31 fetuses at low risk of prenatal thyroid disease and claimed to be an important reference for thyroid size at various gestational ages (Bromley et al 1992), the sensitivity of the nomograms is questionable. Firstly, the method of measuring the fetal thyroid width and circumference included the fetal trachea in both measurements. Secondly, the sample of high risk pregnancies selected to validate the nomograms did not seem to be randomized. In that study, five out of twenty-three fetuses at risk of thyroid disease developed goiter and thyroid dysfunction. The incidence was 21.7%. The overall incidence of congenital hyperthyroidism or hypothyroidism in high risk populations is estimated to be not greater than one percent (Becks & Burrow 1991). The high percentage of fetal goiters detected in their small sample population was unusual and therefore their validation may not be reliable.

If a linear measurement has to be taken to reflect the thyroid size, the mean transverse diameter requiring two measurements is recommended as it is the second strongest parameter ($R^2 = 0.6861$) to correlate positively with gestational age. Due to the anatomical location of the thyroid, the

transverse section will be the measure with the greatest accuracy. The error in determining linear measures in the transverse section was estimated to be below 5% and the error of the longitudinal measurement of the lobe was found to be less than 10% in adults (Szebeni & Beleznay 1992).

Four ultrasonic methods are available for determination of thyroid volume: Ellipsoid Method, Corrected Ellipsoid Method, Numerical Integration and 3-D Ultrasound.

Thyroid volume measurement (V_{lobe} = thickness x width x length x $\pi/6$) by the ellipsoid approximation of separate lobes of the thyroid gland is commonly accepted in spite of its well-known inaccuracy (Himanka et al 1955; Kelly 1954). The systematic error was as high as 20% (Szebeni & Beleznay 1992).

The corrected ellipsoid method, instead of ultilizing the ellipsoid main axes, deduces the volume from the cross-sectional areas which take into account the real shape of the gland. As the real areas are measured, the corrected ellipsoid method gives less than 5% error (Szebeni & Beleznay 1992).

In the numerical integration method, the volume of the thyroid lobes is approximated by the sum of volumes of slices of finite width. By employing computerized semiautomatic digitizing of the outline of the thyroid gland

upon the transverse scans, the areas of the transverse sections are calculated. Volume measurement is then obtained by numerical integration performed along the length of the longitudinal section (Rasmussen & Hjorth 1974). The volume established by this method also gives less than 5% error (Szebeni & Beleznay 1992).

Three-dimensional (3D) ultrasonography had been shown by several studies to be accurate in volume measurements of the prostate gland, kidneys and abdominal organs in vitro and in vivo for adult size (Gilja et al 1994; Gilja et al 1995; Elliot et al 1996), but there are no reported data concerning this method as applied to the fetal organ volume measurements. 3D ultrasound offers various imaging modes in which surface rendering gives detailed plastic images if there are surrounding layers of different echogenicity allowing for the definition of a certain threshold, transparent modes provide an imaging of interior structure of an object, and digital documentation of whole volumes is said to enable full evaluation without loss of information. Although 3D technology provides an increased number of technical options, its applications have to be evaluated for their diagnostic significance and limitations in obstetrics and gynecology (Steiner et al 1994).

For the numerical integration and the three-dimensional ultrasonography methods, specific equipment other than the available conventional real-time ultrasound scanners is required to perform volume

measurements. The equipment for the former method is outdated while for the latter it is not freely available and its clinical application is still under investigation. Due to the unavailability of such kind of equipment in our department, I excluded the last two methods from my study.

Although thyroid volume calculated by the conventional ellipsoid approximation involved about 20% systematic error and the accuracy could be improved by the corrected ellipsoid method or numerical integration (Rasmussen & Hjorth 1974; Szebeni & Beleznay 1992), the ellipsoid method was still employed for two reasons. Firstly, the corrected ellipsoid method utilizing the cross-sectional areas of the three orthogonal planes is technically difficult in a small thyroid lobe. The measurements of the longest axes in the ellipsoid method only involved two perpendicular planes and were technically easier. Secondly, the numerical integration required a manual compound scanner which was not available in our department.

4.1.2 Determination of Maternal Thyroid Status in the Thyrotoxic Population - by biochemical tests

The use of fT_4 and sensitive sTSH measurements is recommended to define the thyroid status of pregnant women (McDougall 1989; Seely & Burrow 1994). However, not all of the pregnant women included in our thyrotoxic population had both tests done for the determination of thyroid status. The maternal thyroid status was defined usually depending on the type of thyroid function test that was available.

In the untreated mothers, the thyroid status was determined by the sTSH assays due to its high sensitivity in detecting suppressed TSH level in hyperthyroidism.

In treated mothers, the thyroid status was decided primarily on the value of the fT_4 rather than the sTSH. Although many studies indicate that sTSH measurements distinguish hyperthyroid as well as hypothyroid from euthyroid patients by detecting the very low TSH levels encountered in hyperthyroidism, it is not entirely specific for hyperthyroidism. A subnormal sTSH may be recorded in the mothers under treatment because the reset of pituitary TSH secretion can take weeks to reach a new steady state between fT_4 and TSH when treatment begins. Therefore sTSH is less useful than direct thyroid hormone measurements in establishing degrees of hyper- or hypothyroidism and correctly reflect the momentary thyroid status (Bayer 1991).

On 24 occasions, FTV could not be correlated with recent maternal thyroid function test (ie. within 14 days). This was always because of maternal disease remission and lack of clinical symptoms. These mothers did not have 4-week follow-up intervals in the clinic. In such cases, normal maternal thyroid function was assumed to be present at the time of ultrasound scans.

4.2 Findings and Observations

4.2.1 Technical Considerations

It has not been mentioned in the literature that the FTV can be measured in the normal fetus. This study, however, showed that FTV could be confidently identified and measured by the high-resolution ultrasound between 20 and 36 weeks. The success rate was over 90% but fell towards late gestation. The main reasons for failure were persistent fetal occipito-frontal position, hyperflexed fetal neck, oligohydramnios and fetal thyroid gland obscured by maternal umbilical shadow. As the fetal head started to engage after 36 weeks, FTV measurements were not always possible because the fetal neck may be obscured by the maternal pubic bone or the fetal neck was hyperflexed to hide the thyroid gland.

4.2.2 FTV in Normal Population

In a normal developing fetus, the fetal thyroid hormone concentration is a reflection of maturation of thyroid function, which is in turn closely related to the total number of functioning units, follicles or acini, formed in the developing fetal thyroid gland (Ingbar 1987). Therefore the greater the number of follicles present in the developing thyroid gland, the more mature and larger the gland will be.

It has been shown in a study of 107 thyroids taken at necropsy from patients aged from 1 day to 93 years who did not have any history of

endocrine disease that the total number of acini in the gland did not show any great change with age. This finding implies that the volume changes of the thyroid gland at later ages of life are a result of changes in the size of the individual acini (Brown et al 1986). It is therefore reasonable to assume that the size of the normal fetal thyroid is related to the fetal thyroid hormone concentrations, a reflection of maturation of thyroid function, which is dependent on the number of acini present.

Maturation of thyroid function can be divided into three phases: embryogenesis (Phase I), hypothalamic maturation (Phase II) and maturation of thyroid system function (Phase III). The process requires a complex coordinated series of events involving the hypothalamus, the pituitary, the thyroid gland and most peripheral tissues, starting in the first trimester (Fisher 1983).

Embryogenesis (Phase I) occurs during the ten to 12 weeks of gestation. During this period, the fetal thyroid gland develops morphologically, accumulates and concentrates iodine, and begins to synthesize iodothyronines. Both fetal sTSH and T_4 are detectable at this time but remain at relatively low level until about 16-18 weeks (Fisher 1983; Blackburn & Loper 1992) .

Hypothalamic maturation (Phase II) starts from four to about 35 weeks. TRH is detected in the hypothalamus by ten to 12 weeks by

radioimmunoassay and in fetal blood in the third trimester (Blackburn & Loper 1992). Histologic maturation of the hypothalamic pituitary portal system is largely completed by 30 to 35 weeks of gestation (Fisher & Polk 1994).

Maturation of thyroid system function (Phase III) begins at mid-gestation and continues until term. A sharp rise of sTSH to a peak at 24 to 28 weeks is initated by a surge of iodine uptake by the fetal thyroid at 20 weeks' gestation. The increase in sTSH is followed by a progressive increase in serum T_4 (Fisher 1983; Wigglesworth & Singer 1991; Blackburn & Loper 1992). After 30 weeks, the sTSH level gradually falls until term indicating that the fetal hypothalamic-pituitary-thyroid axis is fully functional (Fisher et al 1977). However, one recent study disagrees with these findings and shows that the sensitivity of the fetal pituitary gland to negative feedback inhibition by the rising T_4 level is limited and is counterbalanced by increasing stimulation by TRH from the hypothalamus (Thorpe-Beeston et al 1991).

This study found that a positive correlation existed between the normal FTVs and GA in Phase III. The progressive increase in fetal thyroid size after 20 weeks did reflect the complex process of maturation of the thyroid system taking place throughout the gestation (Figure 10). In fact, the growth trend of FTVs is similar to the increase in fetal serum T_4

concentrations with gestation as demonstated by Thorpe-Beeston et al in 1991a.

It was also found that FTV was significantly and independently correlated to other growth parameters such as BPD, FL, AC, and EFW with similar strength. Multiple regression analysis showed that only GA and EFW were significantly correlated to FTV in which EFW dominated the effect. The results were consistent with the role of thyroid hormone in stimulating somatic growth, development of the central nervous system, skeletal and lung maturation (Hobel 1980; Seely & Burrow 1994). The positive correlation of body weight with thyroid volume had been reported by several studies on neonate, child and adult (Hegedüs et al 1983; Berghout et al 1987; Ueda 1990; Chanoine et al 1991).

Sex difference in the FTV was not compared in this study but it has been reported that there was no significant difference in the thyroid size between the female and male neonates although the volume appeared slightly higher in boys than in girls (Chanoine et al 1991).

4.2.3 FTV in Population At-risk

It is well-recognized that the fetal thyroid is likely to be affected by the placental transfer of maternal agents in the thyrotoxic population. Although all the fetal thyroids included in this study from the thyrotoxic population had FTVs fallen within the normal range, there was a noticeable difference in the distribution of FTVs in the treated and untreated groups with different maternal thyroid status.

Furthermore, no fetus in the at-risk group developed a thyroid that had a FTV outside the normal range. This is in agreement with the estimation of only a one percent chance of developing hyperthyroidism or hypothyroidism in fetuses of mothers with active or past Graves' disease (Blackburn & Loper 1992, Burrow 1995). As there were only 72 fetuses in the at-risk group, it is not surprising that not even one goitre was found. Conversely, the 21% possibility demonstrated by Bromley et al should have resulted in about 15 fetuses or neonates with goitres.

Although there was no significant correlation between fetal and maternal thyroid hormone and TSH in the normal population (Thorpe-Beeston et al 1991), a strong correlation between fetal and maternal T_4 levels had been established in Graves' disease (Momotani et al 1986). Maternal T_4 level is hence a useful index of fetal thyroid status in the thyrotoxic population because the fetal thyroid is affected by the same

maternal stimulatory and inhibitory factors including the antithyroid treatment.

In the treated group (irrespective of whether the mothers had normal or abnormal thyroid function), the variation of FTVs around the mean was less than that in the untreated group. It seemed that antithyroid treatment had regularized the fetal thyroid growth.

The relatively consistent growth trend of the fetal thyroids in the treated hyperthyroid and hypothyroid mothers was not expected as abnormal maternal thyroid function should reflect suboptimal treatment and thereby increase the risk of fetal thyroid enlargement. The unexpected observation could be due to the fact that abnormal thyroid function in these ten mothers was mostly transient, and maybe as a result of temporary mal-adjustment of the antithyroid drug dosage.

In the untreated mothers, great variation of FTVs was shown in both groups in which normal and abnormal maternal thyroid function were present. The FTVs in the hyperthyroid mothers were more on the higher side above the mean. In the five hyperthyroid mothers, four had subclinical or mild hyperthyroidism suggested by suppressed sTSH values (<0.03mIU/l) but normal fT_4 level (Kaplan 1985; Bayer 1991). These findings give further evidence to support the potential effects of maternal Graves' disease on fetal thyroids, especially in cases where the mothers have had surgical or

radioactive iodine thyroid ablation. The mothers may not have active thyrotoxicosis and may be euthyroid or hypothyroid, but high levels of TSIg persist after thyroid ablation. The fetus may be affected by the placental transfer of maternal TSIg throughout the pregnancy without the modifying effects of fetal serum levels of maternally administered antithyroid medications (Bruinse et al 1988; Sipe & Malee 1992: Burrow 1995). It has been shown that maternal TIIg levels correlated with fetal T_4 levels in the untreated mothers (Momotani et al 1986). The FTVs of the five mothers who were on L-T_4 replacement did not differ in size from the rest of the fetal thyroids as would be expected from the known relative impermeability of the placenta to maternal T_4 (Vulsma et al 1989) and absence of its effects.

Extensive studies had been performed to show the effects of antithyroid treatment on the fetus. It has been suggested that thionamides may induce in utero hypothyroidism by its high placental permeability with an incidence of ~1% (Burrow 1978). The administration of MMI to pregnant women has been associated with aplasia cutis congenita in the offspring (Kalb & Grossman 1986). However, previous studies have shown that untreated hyperthyroidism resulted in a higher rate of congenital anomalies than did treatment with antithyroid drugs. The risk of uncontrolled maternal thyrotoxicosis is greater than that of high-dose thionamide therapy. In infants of women who were hyperthyroid in the first trimester, the incidence of congenital anomalies was significantly higher than in infants of mothers who were euthyroid in the first trimester. In addition, hyperthyroidism is best

treated prior to conception because the outcome for early treatment before pregnancy is better than that for treatment administered during pregnancy (Davis et al 1989).

In a study of 643 infants of hyperthyroid mothers who were treated with MMI or underwent subtotal thyroidectomy before and/or during pregnancy, six were found to have fetal malformations such as malformation of the ear-lobe, omphalocele, imperforate anus, anencephaly, harelip, and polydactyly. Two out of 243 infants were from the treated mothers and four out of 400 infants from untreated mothers. The respective incidence was 0.8% and 1.0 % for the treated and untreated cases. (Momotani et al 1984;)

In the days before therapy was available for hyperthyroidism, the perinatal mortality was as high as 48% (Ramsay 1991). Therefore the beneficial role of antithyroid drugs far outweigh their teratogenic effect. It is believed that most cases of fetal thyrotoxicosis are probably adequately treated if the mothers are receiving antithyroid treatment (Bruinse et al 1988). The optimal dose should be the lowest dose that can keep the maternal T_4 level in the high normal or slightly elevated range for good fetal outcome (Momotani et al 1986).

This study showed that antithyroid treatment appeared to normalize the fetal thyroid growth in the treated group by demonstrating less fluctuation in size when compared to those in the untreated group. The

observations were compatible with the beneficial role of antithyroid drug treatment suggested in previous studies.

4.2.4 Rate of Fetal Thyroid Growth

The growth of normal fetal thyroid glands increased exponentially with gestational age. The rate of thyroid growth was 5 times faster in late than in mid-gestation. The weekly increase was approximately 0.054cm^3 after 32weeks. It is thought that the mechanism for initiating maturation of the fetal thyroid axis is an increase of TSH secretion in midgestation (Hobel 1980). The fetal TSH concentrations rise and plateau between 20 and 30 weeks followed by a rise of T_4 concentrations (Fisher 1983; Becks and Burrow 1992). These findings agree with the observations of this study in which the fetal thyroid growth accelerated markedly between the 24-27 week period (0.017cm^3/week) and the 28-31 week period (0.031cm^3/week) (see Table 7) (Figure 23).

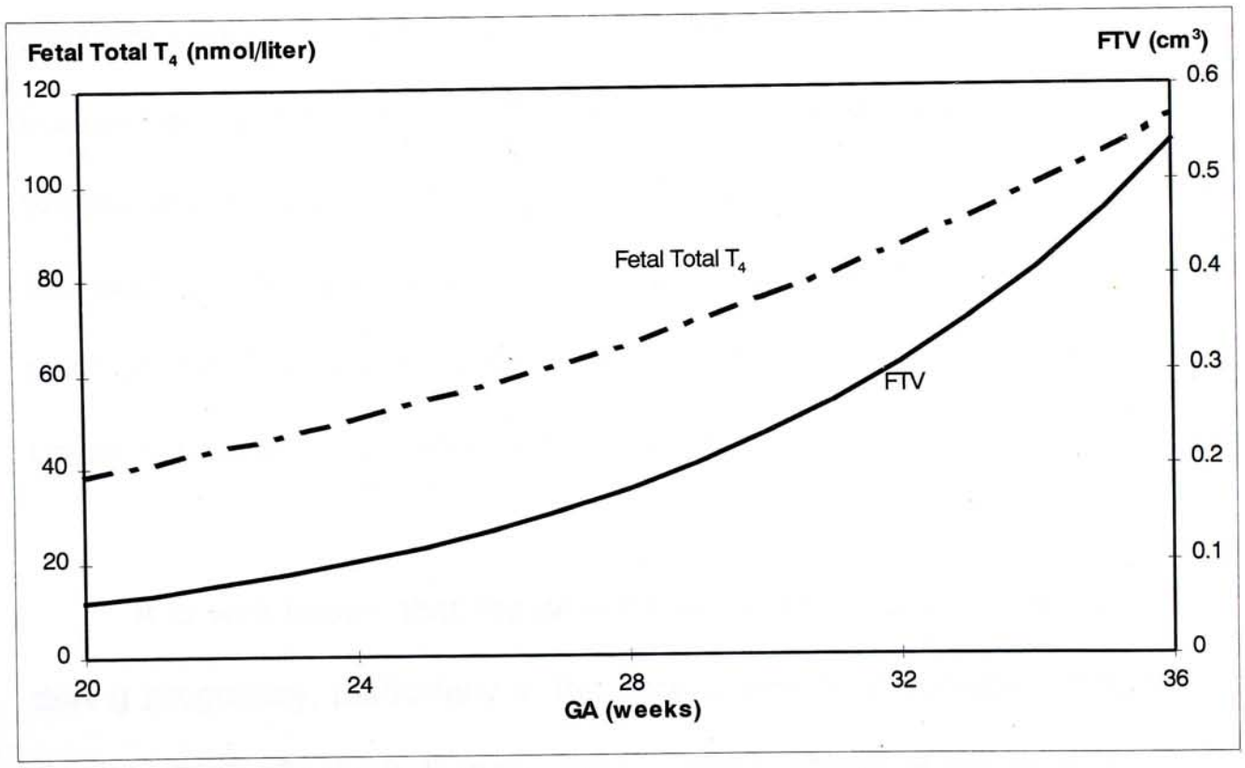

Figure 23. Comparison of the trend of mean FTVs and Fetal Total T_4 at different gestational ages (*curve of fetal total T_4 is taken from the graph of Thorpe-Beeston et al in 1991)*

When comparing the growth rate of FTV in the treated and untreated mothers of the thyrotoxic population with that of the normal population in the same period of gestation, a slight but insignificant difference of fetal thyroid growth rate existed between them. The untreated group had the highest growth rate ($0.055cm^3$/week) compared to the treated which had the lowest ($0.051cm^3$ /week) with the normal in between.

It is recommended to use the lowest possible dose to maintain a maternal euthyroid or mildly hyperthyroid state, mild compromise of fetal thyroid function cannot be totally excluded because the dose for optimal maternal thyroid status may be excessive for the fetus. In our centre PTU is prescribed more frequently than CMZ for treatment of thyrotoxicosis during pregnancy. It has several advantages over CMZ as the drug of choice in pregnancy such as inhibition of extrathyroidal conversion of T_4 to T_3 efficient lowering of T_4 levels, no known side effect of aplasia cutis, less placental transfer and breast milk excretion (Cooper 1984; Cooper 1987). However, this study seems to suggest that there is little difference between PTU and CMZ on the FTVs as these are evenly distributed and close to the mean. Larger numbers would be required for a more confident conclusion.

It is well known that the severity of Graves' disease is ameliorated during pregnancy, particularly in the second and third trimesters (Becks & Burrow 1991; Seely & Burrow 1994). PTU effects must be monitored carefully, particularly during the third trimester when remission can lead to

decreased thyroid hormone production and decreased requirements for PTU (Blackburn & Loper 1992). In the treated group of this study, there were ten mothers who had been found to have transient hypothyroidism or hyperthyroidism, probably as a consequence of the varying severity of the disease and resulting under or over treatment.

4.2.5 Fetal Thyroid Volume to Estimated Fetal Weight(V/W) Ratio

For fetal thyroid disorders such as hyperthyroidism and hypothyroidism, IUGR and goitre are the two common presentations in these conditions (Becks & Burrows 1991). The status of a fetus in the at-risk population can be reflected by the V/W ratio. The value will be elevated in case of an affected fetus suffering from low body weight and/or thyroid enlargement.

The values of mean V/W ratio for normal fetuses under 36 weeks (0.161 cm^3/kg) were smaller than those over 36 weeks (this study), and those for the child (0.2cm^3/kg) (Ueda 1990) and the adult (0.274 cm^3/kg) (Hegedüs et al 1983) reported in other studies. The difference in mean V/W ratios may imply that fetal thyroid enlargement is less likely to be evident and underestimation of fetal goiter may occur if postnatal criteria are used. The relatively larger V/W ratio in late pregnancy may reflect a preparation for thermogenesis that will be necessary postnatally.

By simple mathematical deduction, the V/W ratio is directly proportional to FTV and inversely proportional to EFW. It means that the greater is the value of EFW and/or the smaller is the FTV, the lower the V/W ratio will be. The mean V/W ratio depends on the relative percentage difference of the thyroid gland and body weight.

In fetuses, the variation of body weight was wide within a short period of time. The weight of a fetus at 36 weeks of gestation was on the average about 8.6 times of the value at 20 weeks in our population (0.35 kg at 20 weeks; 3.0 kg at 36 weeks). The increase in FTV (0.057cm^3 at 20 weeks; 0.539cm^3 at 36weeks) during the same period of pregnancy was noticeably greater with a factor of 9.5. This disparity is reflected in the change of V/W ratio from about 0.161 cm^3/week before 35 weeks and 0.200 cm^3/week after.

In comparison, weight in normal adults is relatively static and the variation of body weight is much narrower. A study of measuring V/W ratios on a group of 111 normal adults in Copenhagen found that the body weight of the heaviest subject (100kg) was just 2.5 times of that of the lightest (40kg) whereas the proportional difference between the largest (33ml) and the smallest thyroid volume (8ml) was about 4.25 times (Hegedüs et al 1983). The relative percentage difference of body weight and thyroid volume then ended up with a higher ratio in adults and lower ratio in fetuses with intermediate value in children.

From the V/W ratios, the fetus has the smallest thyroid gland compared to the adult and child per unit body weight. This could be related to the different roles of thyroid gland in fetal and postnatal life. In utero, the function of thyroid gland is mainly to produce adequate thyroid hormones to stimulate fetal growth and promote development of the central nervous

system. Thermogenesis is less critical for fetus as the mother's womb is a thermally stable environment.

In postnatal life, the role of thyroid gland will switch to establish autonomous thermogenesis, apart from stimulating growth and development of the central nervous system. The switch is reflected by an acute surge in TSH within the first 30 minutes of postnatal life. This surge induces a sharp increase in total and free T_4 which play a major role of maintaining the body temperature when the fetus emerges in the cold extrauterine world (Burrow 1995).

The thyroid gland will continue these functions in the later human life with the gland slowly growing into the adult size. It has been shown by histometric methods that thyroid volume increases with age during childhood and adolescence, remains fairly constant in younger adults and declines more slowly in older people (Brown et al 1986).

Besides, a study on 50 healthy subjects in a non-iodine deficient area reported much smaller adult V/W values (male: 0.159cm^3/kg; female: 0.132cm^3/kg) (Berghout et al 1986). These values were even smaller than values for children established by Ueda in a group of normal Japanese children and for fetuses in this study. The mean adult thyroid volume (10.7 cm^3) was also smaller compared to that (18.6 cm^3) of Hegedüs et al with comparable body weight in the two populations. The lower V/W value

demonstrated by Berghout et al should be explained by the smaller mean thyroid volume in their population.

It has been suggested that difference in daily iodine intake, genetic background and environmental factors could contribute to this difference in mean thyroid volume in different geographical areas (McCarrison 1980). Aetiologies of goiter vary but may include iodine deficiency, excessive iodine intake, or other thyroid diseases (Seely and Burrow 1994).

In Japan, a study was conducted in five coastal regions including Hokkaido to evaluate the prevalence of thyroid dysfunction in relation to iodine intake. It was found that hypothyroidism in these areas was more prevalent in thyroid autoantibody-negative subjects with high urinary iodide. The result indicated that the prevalence of hypothyroidism was related to the amount of iodine ingested and marked in excessive iodine intake. In these areas, hypothyroidism may be caused by excessive intake of iodine in addition to chronic thyroiditis (Konno et al 1994). In the study of Ueda, those normal children were living in Hokkaido where iodine-rich seaweed is produced. Since the sampled children were from an iodine sufficient area where diet-induced hypothyroidism was common, it was reasonable to assume that their thyroid volume would be on a higher side to cause a larger V/W ratio than that of the adults from a non-iodine deficient area.

The study of Hegedüs et al was performed in Copenhagen, an area of borderline iodine intake. The urinary output of iodine in Copenhagen area was 80μg in 24 hours (Hegedüs et al 1983) while an excretion rate of iodine greater than 100μg/24hr has been quoted to be the result of an adequate iodine intake (Seely and Burrows 1994). Therefore mild compensatory hypertrophy of the thyroid may be common in Copenhagen.

The same principle may apply to fetuses in Hong Kong. In a recent study done by Kung et al on urine iodine excretion of a group of healthy volunteers (104 children, 112 adults and 349 elderly) in 1996, it was found that 45.3% of the children, 51.7% of the adults and 55.3% of the elderly had urine iodine concentration below the cutoff for iodine sufficiency (0.79 mumol/l). A dietary survey in the same study revealed that seafood was not commonly consumed in our population. Fifty to eighty percent of the subjects never consumed high-iodine containing food such as seaweed, kelp or laver and only fifty percent consumed seawater fish daily (Kung et al 1996). Although Hong Kong is a coastal area where seafood supply is rich, iodine insufficiency does exist.

In fact, high incidence (23%) of transient neonatal hypothyroidism and a relatively high mean cord blood TSH concentration are reported in our population (Kung et al 1997). In the study of Kung et al in 1997, 35.8% of the pregnant women had urinary iodine excretion below the cutoff of 0.79mumol/l. The borderline iodine supply affected the maternal and fetal

thyroid function as demonstrated by a negative correlation between maternal TSH and urinary iodine concentration as well as higher cord blood TSH in those infants whose mothers had a low urinary iodine concentration as compared to those in infants with normal maternal urinary iodine excretion.

As maternal ingested iodine readily reaches the fetus and stimulate the fetal thyroid, persistent deficient iodine supply to the fetus may induce larger fetal thyroid size as a result of compensatory hypertrophy. It is then expected to account for the high fetal V/W ratio when compared with the adult value of Berghout et al.

Furthermore, thyroid disease with goiter is common in our population. In a recent study of 240,000 Hong Kong Chinese children under the age of 15 from 1990 to 1994, there were forty-six Chinese children who had confirmed diagnosis of Graves' disease. The overall incidence was 3.8/100,000/year which was about five times that reported in Danish children (Wong et al 1995). The exact reasons for the high incidence rate in Chinese children in Hong Kong are unknown but larger thyroid size may be expected in the Hong Kong normal population either due to relative iodine deficiency or clinical and subclinical Graves' disease.

Absence of siginificant difference was demonstrated between the V/W ratios of the normal population and the thyrotoxic population including

the subgroups. However, there was a slightly higher value (0.18) noted in the untreated group implying that there was an insignificant number of fetuses in the untreated group who had marginally low EFW and/or marginally high FTVs.

It was found that significant difference was existed between the range of Z scores in the treated and the untreated groups with the range narrower and the values lower in the treated than in the untreated group meaning that the V/W ratios in the treated group were relatively constant. As an elevated V/W value may reflect either fetal thyroid enlargement or IUGR or both, the lower Z values obtained in the treated group would indicate this group of fetuses was less likely to have fetal goiter and/or IUGR. This observation further supports the benefit of antithyroid treatment in the active thyrotoxic mothers.

4.2.6 Intrauterine Growth

Even with treatment, there are slightly more stillbirths and neonatal deaths in the thyrotoxic population than in the normal population and the mean birth weight was found to be lower than those born to normal women (the mean birth weight of white babies was 363g lower and of black babies 184g lower than those born to normal women) (Ramsay ID 1991). A study of two hundred and thirty pregnant women with Graves' disease also demonstrated a slight increase in the neonatal mortality rate and a significant increase in the frequency (6.5%) of delivery of LBW infants (Mitsuda et al 1992). This study is in agreement with the reports above. An 11.5 per cent frequency of LBW infants was encountered with birth weight at or below 2.5kg at term. During the period 95 to 96, the incidence of LBW infants overall was 3.64% (500 in 13,727 infants).

Small babies were more common in this thyrotoxic population than in our normal population. The incidence of LBW infants in Hong Kong Chinese is low. In a previous study this was 2.9% as compared to 4.3% in Hong Kong British (Lyon AJ 1987). Although LBW neonates tend to be less common in Chinese pregnancies than in Caucasian pregnancies, it seems that this is not the case for thyrotoxic pregnancies. In fact this makes the 11.5% incidence even more striking.

Further, antithyroid drug treatment did regularize fetal thyroid growth, but five of six LBW infants were from mothers who were on antithyroid drug

treatment. Therefore, the regularization of fetal thyroid growth is not by itself sufficient to indicate normal progress of pregnancy. Careful monitoring of fetal growth and fetal well-being is important in thyrotoxic pregnancies.

Chapter 5 Conclusions

Maternal autoimmune thyroid disease, most commonly Graves' disease, is well-known to pose adverse effects on the fetus by the circulating stimulatory and inhibitory autoantibodies or by the medical treatment itself. The affected fetus may develop thyroid dysfunction, growth retardation, fetal abnormalities or in severe case, fetal death. It is therefore essential to diagnose early thyroid disorder in the fetus and apply treatment accordingly. Diagnosis and therapy nowadays can be made by cordocentesis. This is the most accurate but is an invasive procedure. Fetal thyroid ultrasound can be a non-invasive diagnostic test, diagnosing and screening the presence of fetal goiter and monitoring the size after treatment .

In this study, a nomogram for FTV and some related parameters such as FTV growth rate and V/W ratio have been established to serve the purposes stated above. Fetal thyroid size is better reflected by the FTV compared with any other single dimension of the gland. Measurement of FTV is feasible between 20 and 36 weeks of gestation.

From the observations of this study, a better picture was obtained on how the fetal thyroid of a thyrotoxic mother is affected by the maternal thyroid disease with and without treatment. Treatment appears to regulate fetal thyroid growth by showing a more constant growth trend near the mean. Transient variations of the dose of antithyroid drugs with resulting

abnormal maternal thyroid function does not seem to affect the fetal thyroid gland.

The fetuses of mothers with Graves' disease, either active or previously active prior to the pregnancy but not taking any antithyroid treatment, have FTVs more variable in size. In fact, subclinical hyperthyroidism is common in the mothers who have remission of disease post-surgical or radioactive thyroid ablation. Therefore this group of fetuses still warrants attention as the maternal immunoglobulins may still affect the fetus and subsequently the neonate.

In addition, diminished growth is more common in the thyrotoxic than the normal population.

Based on the known risks of maternal Graves' disease, serial fetal thyroid ultrasound is recommended in addition to the routine antenatal scan for every at-risk fetus for monitoring thyroid growth and somatic growth. The nomogram and normal reference for fetal thyroids in this study should be applied to help achieve the best possible outcome.

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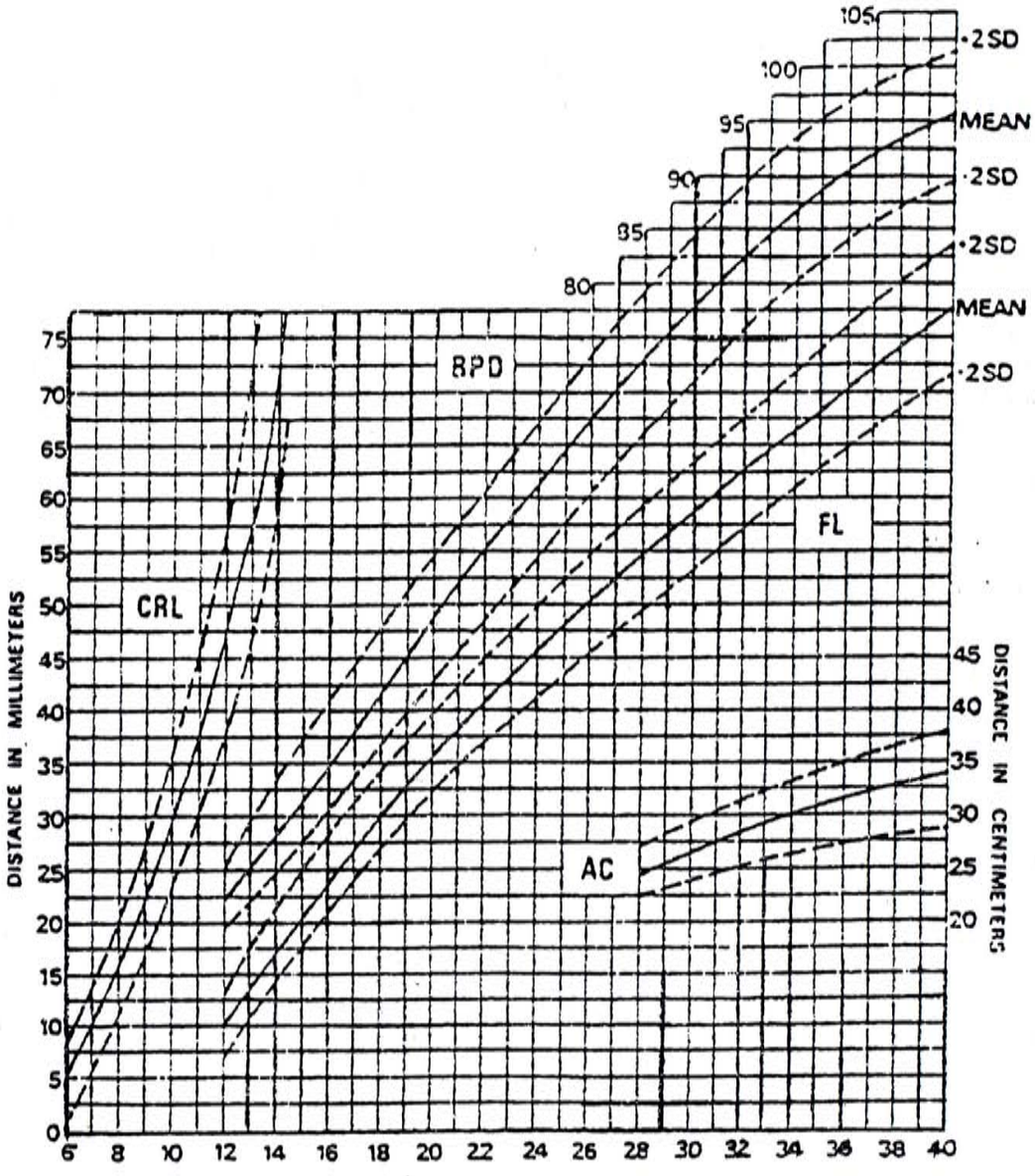
Appendix I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